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INTERMITTENT POSITIVE PRESSURE BREATHING*

Its Use in the Inspiratory Phase of Respiration

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THE therapeutic value of mechanical respiration in acute and chronic pulmonary diseases, as well as in cardiac conditions, has encouraged the development of many types of apparatus, found largely in the laboratories of physiologists and clinicians interested in pulmonary diseases. The numerous mechanical devices successfully used for pressure breathing include face masks, hood domes and body respiratory chambers, which, depending on the method of application, induce different physiologic responses.

Notation System

The factors that enter into all types of pressure breathing are as follows: timing of pressure (intermittent — during inspiration *or* expiration — and continuous — during inspiration *and* expiration); types of pressure (positive — greater than atmospheric pressure — and negative — less than atmospheric pressure); and site of pressure (airway passages, chest wall and a combination of these sites).

For the sake of simplicity we are abbreviating key terms in this list by reducing the component words to their initial letter — for example, the term "intermittent positive pressure breathing in the inspiratory phase" employing the Bennett valve appears as IPPB/I–Bennett. The notation system is summarized in Table 1.

Table 1. *Notation System in Pressure Breathing.**

Timing	Type	Pressure Breathing	Phase of Respiration	Notation	
C = continuous I = intermittent	P = positive N = negative	PB	/I = inspiratory /E = expiratory	code	device
I	P	PB	/I	IPPB/I	Bennett Valve — e.g.
I	P	PB	/E	IPPB/E	Meter Mask — e.g.
I	N	PB	/I	INPB/I	Body Respirator
C	P	PB	/I & E	CPPB/I & E	Hood — Dome
C	N & P	PB	/I & E	C (N & P) PB/I & E	Body Respirator
C	P & N	PB	/I & E	C (P & N) PB/I & E	Eliot Exsufflator Valve — e. g.

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Methods and Equipment

There are two modes of administering pressure breathing differentiated by timing which is either intermittent or continuous.

In the intermittent type the gas mixture is supplied in either the inspiratory (IPPB/I) or expiratory (IPPB/E) cycle, usually through a face mask. Of the several types of mask devices that supply IPPB those most commonly used for IPPB/I alone incorporate the Burns, Mine-Safety Appliance, Emerson or Bennett valve. These valves are automatic flow-sensitive or pressure-sensitive cycling devices, with varying advantages especially related to the type of mask pressure curves that they supply. The Bennett air pressurizing unit can be attached to the basic pressure therapy unit. This enables a supply of filtered room air at controlled pressures for use with the unit, or any desired concentration of oxygen can be obtained by dilution. This is an important safeguard in the management of patients in whom carbon dioxide retention or respiratory acidosis is likely to develop when high concentrations of oxygen are given. Furthermore, it also provides a substantial saving in the cost of oxygen to the patient or hospital.

For IPPB/E only, the O.E.M. Meter Mask[2] or the Respiration Aids Mask is used. The patient

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sets up a gentle positive pressure in expiration by blowing the expired air through the narrowed orifices of the metering disk in the meter mask.

The body respirator — Drinker, Collins or Emerson — is useful for supplying a form of INPB/I, applied to the chest wall; a negative pressure is produced within the chamber during inspiration, whereas expiration is passive. In addition, if considered desirable, the passive expiratory phase may be converted to a positive one, thus establishing a continuous type of pressure breathing: negative in inspiration and positive in expiration applied to the chest wall — C (N&P) PB/I&E — Emerson.

The body types of respirators employing negative and positive intratank pressure in inspiration and expiration respectively have been shown to be the physiologic equivalents of alternating positive and negative mask pressure, so far as their effects on the lungs and circulation are concerned.[3, 4]

The continuous method of pressure breathing supplies air, oxygen or a mixture of helium and oxygen under positive pressure during both the inspiratory and expiratory cycles (CPPB/I & E). The positive pressure enclosing hood apparatus (O.E.M.) or the double-bellow mask (O.E.M.) may be employed for this purpose.[2] The hood requires a tight neck closure, a co-operative patient and considerable technical help for proper management. Many patients object to the double-bellow mask because of the sense of forced breathing in the expiratory phase; in its present form, furthermore, the equipment requires considerable technical care and readjustment of valves.

Birnbaum and Thompson[5] have long stressed the beneficial effects on the circulation of mechanical respirators employing positive-negative pressures. Maloney et al.[6, 7] demonstrated the advisability of the negative pressure phase in expiration in mechanical resuscitation in preventing the drop in arterial blood pressure and cardiac output observed in patients with inadequate circulation when inspiratory positive pressure breathing was employed alone.

Barach and his associates,[8, 9] continuing their studies in developing more practical equipment suitable for eliminating retained secretions in the tracheobronchial tree, "exsufflation with negative pressure," have recently employed a variety of cycling valves with one or two motor units for the positive and negative pressures created in the face-mask piece.[9*] These units permit inspiratory positive pressure with an instantaneous change-over to an extremely rapid expiratory negative pressure. A high expiratory flow rate is thus achieved. The authors have found this form of mechanical respiration life saving in a variety of pulmonary and non-pulmonary diseases, in which secretions have accumulated in the tracheobronchial tree. We[10] have employed the Eliot exsufflator* unit, which was designed according to the principles advocated by Barach and his associates. This portable unit supplies a gradually increasing positive pressure breathing on inspiration. This plateau is reached in 2.48 seconds and is followed by an instantaneous change-over to an extremely rapid expiratory negative pressure — a form of C (P&N) PB/ I & E.

*The Cof-flator, manufactured by the O.E.M. Corporation, East Norwalk, Connecticut, and the Exsufflator, by the Eliot Medical Plastics, Incorporated, Lynn, Massachusetts.

Physiologic Effects

The use of pressure breathing is based on the creation of a pressure gradient from the mouth down to the pleural space. In the inspiratory phase in normal persons, positive pressure through a face mask produces mechanical inflation of the lungs similar in some respects to that caused by negative pressure around the thorax by means of the body respirator. At the height of inspiration, however, the pressure built up in the patient's airway is greater than that built up around the body.[3, 4]

In the expiratory phase, negative pressure by mask normally has the same mechanical and physiologic effects on respiration and circulation as positive pressure exerted by the body respirator — provided, of course, that these counterforces are of equal magnitude.[3, 4, 6, 7]

In emphysematous patients these pressures may not be transmitted as exact equivalents since the equilibrium of the elastic and co-ordinating structures have been upset by the uneven damage of intermediate tissues.[1] We have not observed any evidence of bronchiolar or alveolar rupture with inspiratory positive pressure breathing. It is unlikely that this will occur with the pressures, usually set at 10 to 20 cm. of water, employed with most of the demand cycling valves in use. This is considerably lower than the pressures created when the anesthesia bag is compressed. It has been stated that the normal person develops without harm a differential pressure of 45 mm. of mercury across the lungs in performing the vital-capacity test.[7]

The physician should be familiar with the effects of pressure breathing on the peripheral circulation as well as on the heart. The cardiac output is a true equivalent of the venous return, which in turn depends on the gradient between the peripheral venous pressure and the pressure in the right atrium. Although the cardiac output must be equal for both ventricles in a compensated heart, it becomes physiologically unequal when deep breathing or a Valsalva-like maneuver creates a differential output and pressure between the pulmonary and systemic circulation. For all practical purposes, these variations can be understood if the behavior of the right-ventricle output is understood. When IPPB/I is applied through the mouth by means of a mask, the cardiac output tends to fall during the pressure phase of the cycle, and the net filling pressure of the right ventricle also falls.[11] The opposite holds true for the phase of decreasing mask pressure.[11]

Even under acute experimental conditions, normal persons will react against transient falls in cardiac output by reflex peripheral vasoconstriction in an attempt to reconstitute the venous gradient.[3] The presence of normal sympathetic pathways is therefore necessary to permit this "escape-like" mechanism.

Patients with circulatory inadequacy or in peripheral circulatory collapse as in hemorrhagic shock should not be injudiciously exposed to positive pressure breathing. Peripheral vasoconstriction in these patients has already been utilized to a maximum extent, and a further drop in cardiac output is all that can be expected. In emphysematous patients, however, when there is evidence of shock or loss of the vasoconstrictor mechanism, IPPB/I combined with a negative expiratory phase pressure will help reconstitute the venous gradient and cardiac output as well as prevent a further drop in blood pressure.[9, 10] Similar results can be obtained through application of changing pressure on the chest wall with a body respirator (C [N&P] PB/I&E respirator).

A mask pressure curve of a respiratory cycle was obtained with a Bennett TV–2P valve (Fig. 1). The patient was breathing 100 per cent oxygen, and the pressure was set at 17 mm. of mercury. The duration of inspiration was 1.92 seconds, and that of expiration 2.2 seconds. The mean pressure of the entire respiratory cycle was 5.72 mm. of mercury. The smooth action of the valve in following the breathing effort of the patient is seen in the linearity of the inspiratory and expiratory curves. This curve is similar to the Type 3 curve obtained by Cournand et al.[11]

From the foregoing it will be seen that inspiratory positive pressure breathing overcomes the bronchial resistance and widens the bronchi; helps establish a more efficient cough; creates a more uniform alveolar aeration, thus improving intrapulmonary mixing; reduces residual volume; improves the ventilation-perfusion relation by virtue of the more uniform alveolar aeration and the decrease in residual volume; prevents or minimizes the outward filtration through the capillary membrane; and diminishes the blood volume returning to the right side of the heart, with a subsequent drop in cardiac output and blood supply to the lungs.

Clinical Application

Bennett Valve

We have studied a total of 203 patients who were treated with IPPB/I — Bennett valve — for the following disorders:

Bronchial asthma. Ninety-five patients with different grades of severity.

Chronic pulmonary emphysema. Seventy-four patients, many of whom had chronic pulmonary emphysema secondary to long-standing bronchial asthma.

Bronchiectasis. Twenty patients with unilateral or bilateral disease, 3 of whom had previously undergone lobectomy.

Pulmonary edema. Four cases due to cardiac failure.

Irritating gases and fumes. Three patients with bronchial and bronchiolar irritation and congestion from the inhalation of irritating gases and fumes.

Respiratory depression. Three patients with barbiturate intoxication, and 1 with a combination of morphine and barbiturates (these patients were in coma, with marked respiratory depression and peripheral circulatory failure, and in 1 case respiratory acidosis — carbon dioxide intoxication — was demonstrated.

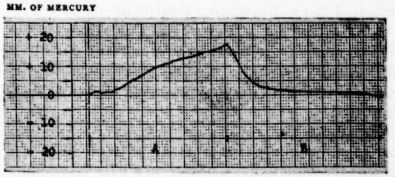

FIGURE 1. *Mask Pressure Curve Obtained with IPPB/I, Bennett TV-2P Valve.*
Inspiration (A) = 1.92 seconds, and expiration = 2.2 seconds. Mean pressure of entire cycle = +5.72 mm. of mercury.

Chest trauma. Three patients with fractures of the chest cage and muscle injury that interfered considerably with breathing and coughing.

Technic

A Bennett apparatus (model TV–2P)* providing intermittent positive pressure on inspiration (IPPB/I) with an attachment permitting the use of a plastic Vaponefrin nebulizer fed by separate low oxygen flows was used. The patient is encouraged to breathe slowly and deeply. The instantaneous flow rate is high enough for the patient who is greatly hyperventilating and has a large tidal volume, whereas the flow-sensitive valve permits the patient with emphysema, for instance, to exhale at will before a new inspiratory cycle begins.

Either air or oxygen was used in these treatments, with or without a bronchodilator solution in the nebulizer. A pressure of 15 to 20 cm. of water was tolerated by all the patients except those in status asthmaticus. In these patients it was preferable to initiate treatment with a low pressure of 5 to 10 cm., with a gradual increase. One cubic centimeter of a bronchodilator solution (Neosuprel, Isuprel or Vaponefrin) was used in most cases. For patients with a superimposed bronchiolar infection a suitable antibi-

*Manufactured by V. Ray Bennett and Associates, Incorporated, Los Angeles.

otic was added to the aerosol solution — in some patients in addition to parenteral administration. Pancreatic Dornase,* a desoxyribonuclease of pancreatic origin, was given by the aerosol route to patients who had very viscous sputum.[12] This pus-liquefying enzyme thinned the sputum and facilitated expectoration of the bronchial secretions.

Treatments were usually given once or twice daily and in some cases three times a day. The duration of a single treatment averaged about 20 minutes, and that of a course of treatment from 5 to 60 days. The patients with bronchiectasis or chronic pulmonary emphysema were advised to return monthly for 2 to 4 days of intensive treatment.

The Bennett apparatus is equipped with a manual control whereby inspiration and expiration can be initiated at will. This attachment is of considerable value in patients with respiratory depression or standstill.

The results of treatment were evaluated clinically and also by means of several determinations of pulmonary function. Clinical evaluation included the patient's subjective feeling, chest examination for rales and wheezes, changes in cough and expectoration and exercise tolerance. For objective observations we used the vital capacity, maximal breathing capacity and timed vital capacity, the technic of which is described elsewhere.[13, 14] Similar extensive studies with IPPB in chronic pulmonary disease have been made by Motley and Tomashefski,[15] Smart, Davenport and Pearson[16] and Gordon and his associates.[17]

TABLE 2. *Clinical Results in 105 Patients with Bronchial Asthma, Pulmonary Emphysema or Bronchiectasis Treated with IPPB/I.*

Grade of Disease	No. of Patients	No Change	Slight Improvement	Good Results	Excellent Result
		no. of patients	no. of patients	no. of patients	no. of patients
Bronchial asthma:					
Moderate	21	—	2	10	9
Severe	32	—	1	18	13
Totals	53	—	3	28	22
Pulmonary emphysema:					
Moderate	24	—	1	20	3
Severe	20	2	5	9	4
Totals	44	2	6	29	7*
Bronchiectasis:					
Moderate	5	—	—	2	3
Severe	3	—	—	2	1
Totals	8	—	—	4	4

*Two of these patients subsequently died of progressive pulmonary insufficiency.

RESULTS

Clinical Results

Bronchial asthma. Ninety-five patients with different grades of bronchial asthma were treated with IPPB/I with or without bronchodilator aerosols. It was noted that the therapy generally helped in this group of patients by diminishing their respiratory distress, as indicated by less wheezing and cough. Detailed observations on 53 of these patients were recorded (Table 2). Improvement after treatment was observed in all cases: 3 patients improved slightly, 28 showed good results, and 22 were relieved of all symptoms.

Chronic pulmonary emphysema. Seventy-four patients with chronic pulmonary emphysema, secondary to chronic bronchial asthma in many cases, were treated. These patients showed improvement in color owing to better oxygenation. Cough eased, and expectoration was performed with less difficulty. The breathing pattern became more regular, and exercise tolerance increased.

Detailed observations on forty-four of these patients appear in Table 2. Two patients did not give evidence of improvement. Six improved slightly; 29 showed good results, and 7 excellent results. Two patients subsequently died from progressive pulmonary insufficiency.

Bronchiectasis. Twenty patients with bronchiectasis, 3 of whom had previously had lobectomies, were treated. In all cases the end results were very good. There was greater ease of expectoration and an initial increase in the amount of sputum. This decreased as the treatment was continued and cough became less severe. The recurrent pulmonary infections seemed to be more favorably influenced by this form of treatment. The patients showed increased exercise tolerance. Many of these patients received, in addition to the IPPB/I, aerosols of Pancreatic Dornase for liquefaction of the sputum.

Clinical observations on 8 of these patients are recorded in Table 2. The results were considered good in 4 and excellent in 4 others.

Miscellaneous pulmonary conditions. IPPB/I was used successfully in various pulmonary emergencies. Pulmonary edema due to the inhalation of irritating gases and fumes was rapidly relieved in 3 patients. Four patients with cardiac failure and pulmonary edema were treated for several hours. Treatment was given for thirty minutes, alternating with twenty-minute rest periods. Results were moderately good during treatment. However, pulmonary edema recurred shortly after treatment was discontinued.

Three patients with chest trauma were treated. They were severely ill and cyanotic, and secretions had accumulated throughout the tracheobronchial tree. Because of pain and the consequent administration of narcotics, the cough reflex was depressed. Aspiration of secretions with a tracheal catheter was ineffective. Treatment with IPPB/I appeared to be life saving.

Three patients with respiratory depression from barbiturate intoxication and 1 with respiratory depression due to a combination of morphine and barbiturates were treated. These patients were in coma, with marked respiratory depression and

*Available from Sharp and Dohme, Incorporated, West Point, Pennsylvania.

peripheral circulatory failure. Treatment was given for several hours intermittently until all the toxic effects on the respiratory center had diminished sufficiently to allow the patient to ventilate without mechanical help. Most gratifying results with IPPB/I were observed in a patient who, in addition to chronic pulmonary emphysema and the syndrome of carbon dioxide intoxication, had cardiac failure; manifestations of carbon dioxide intoxication had been noted several times during injudicious administrations of high concentrations of oxygen just before this study.

This patient was subjected to six consecutive hours of IPPB/I (Table 3), room air being used.

Laboratory Results

Comparison of bronchodilator aerosols alone with IPPB/I in addition to bronchodilator aerosols. The effects of IPPB/I with simultaneous administration of a bronchodilator* by aerosol were compared with those of the bronchodilator aerosol alone on patients with bronchial asthma grouped according to the severity of their bronchospasm (Table 4). The data indicate that the combination of IPPB/I with a bronchodilator aerosol is superior, as measured by improvement in the vital capacity, to a bronchodilator aerosol alone. There was an additional average increase of 150 to 300 cc. in

TABLE 3. *Correction of Respiratory Acidosis with Intermittent Positive Pressure Breathing.**

	Phase	Minimum Ventilation	Respiratory Rate	Pulse	Arterial Blood†					
					Carbon Dioxide Tension	Oxygen Tension	Buffer Base	Oxygen Saturation	Chloride	pH
		liter/min.			mm.Hg.	mm.Hg.	milliequiv./liter	%	milliequiv./liter	
I	a) Control	5.500	16	88	69	40	63	74.58	92	7.40
	b) 5% CO_2, 95% O_2 at 2-liter flow for 7 min.	5.300	17	80	63	62	61	89.48	92	7.40
II	a) Control		17	82						
	b) 100% O_2 for 72 min.	3.300	22‡	84	89	76	59	91.83	93	7.28
III	a) Control	3.300	22	84	89	76	59	91.83	93	7.28
	b) IPPB compr. air, 15 cm. H_2O for 2 hr.	8.400	18	84	72	59	60	85.69		7.35
	c) At 6 hr.		16	84	65	49	61	82.94	97	7.39

*Based on Segal and Dulfano.[1]
†Hematocrit — 40%.
‡Shallow.

Starting from the control point (Phase III*a*), the rise in minute ventilation was sufficient to correct the increased arterial carbon dioxide tension and restore the pH to normal levels (Phase III*c*). These values had been thrown out of balance by previous administrations of high oxygen concentrations that had been given specifically to show the patient's susceptibility to respiratory acidosis (Phase II*b*). The rise in minute ventilation prevented the respiratory acidosis usually noted in this patient when high concentrations of oxygen were administered by conventional mask therapy.

TABLE 4. *Average Improvement in Vital Capacity after Use of 1.0 cc. of Bronchodilator and after IPPB/I with Simultaneous Use of 1.0 cc. of Bronchodilator in Patients with Bronchial Asthma.*

Degree of Bronchospasm	Effect of Bronchodilator Alone		Effect of IPPB/I with Bronchodilator	
	No. of Patients	Average Increase in Vital Capacity	No. of Patients	Average Increase in Vital Capacity
		cc.		cc.
0	36	148	7	300
+	56	311	8	550
++	34	369	11	718
+++	6	650	6	800

the vital capacity after the combination of therapy in all the groups treated. Instead of the 20 per cent improvement in maximal breathing capacity averaged with IPPB/I and aerosols, the same group of patients averaged only a 10 per cent improvement when they used the same bronchodilator alone by hand nebulization.

Comparison of IPPB/I alone with IPPB/I in addition to bronchodilator aerosols. The determinations of timed vital capacity and the maximal breathing capacity were made in the three major groups of patients with bronchial asthma, chronic

TABLE 5. *Average Maximal Breathing Capacity after IPPB/I Alone and in Combination with 1.0 cc. of Bronchodilator.*

Diagnosis	Maximal Breathing Capacity			Increase with Combined Therapy over Control
	Control	IPPB/I	IPPB/I combined with Aer.	
	liters/min.	liters/min.	liters/min.	%
Bronchial asthma	41.6	40.1	60.6	45.7
Emphysema	34.9	34.4	47.3	35.5
Bronchiectasis	55.1	42.7	68.9	25.0

*5 per cent 1313 (Dapanone), available from Sharp and Dohme, Incorporated, West Point, Pennsylvania.

pulmonary emphysema and bronchiectasis (Tables 5 and 6). These measurements were taken after IPPB/I alone and after IPPB/I with bronchodilator aerosols in the same patients. The results indicated that IPPB/I alone, despite the beneficial effects observed clinically, caused a decrease of the maximal breathing capacity in 60 per cent of the determinations and of the timed vital capacity in 80 per cent.

TABLE 6. *Effect of IPPB/I and IPPB/I with Bronchodilator on the Timed Vital Capacity and Ratio (Average Values of 100 Treatments).*

TREATMENT	1ST SEC. VITAL CAPACITY	TOTAL VITAL CAPACITY	RATIO OF 1ST SEC. TO TOTAL VITAL CAPACITY	CHANGE	
				1ST SEC.	TOTAL VITAL CAPACITY
	cc.	cc.	%	%	%
Control	1189	2309	52	—	—
IPPB/I	745	1958	39	−16	− 8
IPPB/I with aerosol	1353	2649	51	+18	+17

In addition, there was a marked decrease of the already low ratio of first-second to total vital capacity: from 52 per cent to 39 per cent after IPPB/I. IPPB/I with bronchodilator aerosols as compared with IPPB/I alone improved measurements markedly. The combination treatment improved the maximal breathing capacity 45.7 per cent over the control in bronchial asthma, 35.5 per cent in chronic pulmonary emphysema and 25.0 per cent in bronchiectasis (Table 5).

The first-second of the timed vital capacity decreased 16 per cent after IPPB/I but increased 18 per cent after the combination treatment. The total vital capacity decreased 8 per cent after IPPB/I and increased 17 per cent after the combined treatment. Because both the first-second and the total vital capacity improved to the same degree, there was no essential change of the ratio — from 52 to 51 per cent (Table 6).

Long-term treatment with IPPB/I. Measurements were recorded on a group of 10 patients with chronic pulmonary emphysema who were given one or two treatments a day over a period extending from 30 to 60 days. Table 7 shows for each patient the average vital capacity during the entire course of treatment and that during the first and last 5 days of treatment. Treatment consisted of IPPB/I alone and IPPB/I with bronchodilator aerosols. These two forms of treatment were given consecutively with intervals of half an hour to one hour. It was again noted that the vital capacity decreased after IPPB/I alone in the majority of patients (Table 7), averaging −7.8 per cent in the 10 patients. In contrast the combination of IPPB/I with bronchodilator aerosols increased the vital capacity in all patients, averaging +31.0 per cent for the entire group.

The use of IPPB/I with bronchodilator aerosols improved the vital capacity of these patients from an average of 1939 to 2468 cc. (Table 7), but prolongation of treatment did not have any additional benefit as measured by the vital capacity, from an average of 1975 to 2543 cc. The average values obtained during the last 5 days of treatment of an extended course were within narrow margins similar to those obtained during the first 5 days (Table 7).

DISCUSSION

Most of the effects of IPPB/I on pulmonary ventilation can readily be understood. With the mechanisms previously discussed in mind, it is almost possible to predict the effect of IPPB/I in certain medical conditions.

In bronchial asthma, in which bronchospasm and bronchial obstruction are among the major factors contributing to the patient's discomfort, it was anticipated that IPPB/I would be beneficial. The clinical results corroborated this assumption. After

TABLE 7. *Changes in Vital-Capacity Averages during Long-Term Treatment of Patients with Severe Pulmonary Emphysema.*

CASE NO.	ENTIRE COURSE OF TREATMENT					1ST 5 DAYS OF TREATMENT			LAST 5 DAYS OF TREATMENT		
	CONTROL VITAL CAPACITY	VITAL CAPACITY ON IPPB/I ALONE	CHANGE	VITAL CAPACITY ON IPPB/I WITH AEROSOL	CHANGE	CONTROL VITAL CAPACITY	VITAL CAPACITY ON IPPB/I ALONE	VITAL CAPACITY ON IPPB/I WITH AEROSOL	CONTROL VITAL CAPACITY	VITAL CAPACITY ON IPPB/I ALONE	VITAL CAPACITY ON IPPB/I WITH AEROSOL
	cc.	cc.	%	cc.	%	cc.	cc.	cc.	cc.	cc.	cc.
1	1290	1255	− 2.8	2500	+94	1220	1300	2520	1200	1080	2460
2	2489	1850	−26.0	3083	+24	2180	1867	2750	2710	—	3340
3	2067	—	—	2192	+ 6	2100	—	2225	2020	—	2125
4	1635	1486	− 9.0	1973	+21	1520	1375	1840	1460	1530	2020
5	2179	1683	−22.0	3229	+48	2447	1467	3117	2117	1900	3350
6	2478	—	—	2628	+ 6	2640	—	2865	2325	—	2582
7	2700	2740	+ 1.4	3242	+20	2466	2700	3034	2934	2767	3450
8	1188	1000	−16.0	1829	+54	1050	950	1800	1325	1025	1800
9	1913	1950	+ 2.0	2025	+ 6	1970	1950	2100	1880	—	2050
10	1800	1986	+10.0	2350	+31	1800	2038	2425	1800	1917	2250
Averages	1899	1744	− 7.8	2505	+31	1939	1705	2468	1975	1703	2543

treatment the patient invariably felt better, his breathing was easier, there was less wheezing as a rule, and the cough was more effective in raising mucus. However, the determinations of the vital capacity, timed vital capacity and maximal breathing capacity made immediately after IPPB/I were usually less than the control value. No definite explanation can be given, although it seems possible that the reflux of blood into the pulmonary tissues after a period of positive pressure breathing causes enough congestion of the pulmonary tissues to produce material interference with these determinations. Also, it seems conceivable that positive pressure breathing alone introduces temporarily a factor of fatigue.

From the data presented it is evident that the combination of IPPB/I with a bronchodilator spray is more effective than the bronchodilator aerosol alone. Gordon and his associates[17] also emphasized the superiority of bronchodilator drugs given with IPPB/I over the same bronchodilator drugs used alone. This is acceptable in view of the fact that the positive pressure, although widening the diameter of the lumens, carries the aerosol into smaller and even obstructed bronchioles. This gives a wider and more effective dispersion of the bronchodilator spray. By this combination we noted an additional increase of 150 to 350 cc. in the vital capacity after the maximum effect from the bronchodilator aerosols alone had been obtained. Likewise, the data demonstrate clearly the superiority of the combination of IPPB/I with bronchodilator aerosols over IPPB/I alone. It seems that the presence of a bronchodilator drug is necessary to overcome bronchospasm as well as to facilitate and to make more lastingly effective the mechanical dilatation of the bronchial tree by positive pressure.

In chronic pulmonary emphysema, in which some of the major defects are decreased lung elasticity and tension, uneven ventilation, increased residual volume and various degrees of bronchoconstriction, beneficial effects from IPPB/I are expected.[1, 15] Improved alveolar aeration, decreased residual volume and more patent bronchial tubes manifest themselves clinically by the results obtained. The relief from distressing symptoms noted by most patients with chronic pulmonary emphysema after treatment with IPPB/I was less dramatic, however, than that experienced by the patients with bronchial asthma or those with chronic pulmonary emphysema and marked bronchospasm. Less dyspnea and distressing cough after treatment and better exercise tolerance after prolonged treatment were observed.

Again, the vital capacity after IPPB/I alone decreased in most patients, and the maximal breathing capacity decreased in some, as in the patients with bronchial asthma. In a group of patients who received IPPB/I with aerosol treatment over a prolonged period the average increase in vital capacity after treatment amounted to 31 per cent of the control value.

It is apparent from this study that prolongation of treatment did not influence the daily control vital capacity or the vital capacity after subsequent treatment. The average determinations during the first 5 days of treatment (control and after treatment) were similar to those made at the end of a course of treatment. Thus, it seems that a single treatment gave the patient with chronic pulmonary emphysema the maximum improvement in vital capacity that could be noted. However, clinical improvement was noticeable and was maintained for a long time after 20 to 30 days of treatment. The "plateau" of improvement in pulmonary function reached at this time could not be influenced further by prolongation of treatment, but a monthly "booster" treatment of 2 to 4 days helped to prolong the patient's comfort.

In patients with bronchiectasis the areas involved in the chronic process of infection and tissue destruction do not ventilate adequately. Drugs given by aerosol, therefore, do not always reach the parts of the lung that need them most. It was anticipated that IPPB/I would disperse the medication into all parts of the tracheobronchial tree, regardless of the degree of ineffective ventilation. Apparently, the antibiotics and the polymerizing enzyme carried in a vehicle of bronchodilator action reached the bronchiectatic areas. As a rule, the very first treatment was followed by copious 24-hour expectoration, which continued for several days until draining was complete. Then the cough and the expectoration gradually subsided.

Patients who have been severely exposed to irritating gases or fumes should be given IPPB/I treatment prophylactically whenever possible. Its beneficial effect, even after pulmonary edema has occurred, is often striking. Maintaining adequate ventilation is indicated and is effective by means of IPPB/I in patients with respiratory depression. Respiratory acidosis will correct itself when ventilation is improved, and the depressing effects of the drug will eventually wear off. When respiratory depression is caused by morphine, its derivatives or similar drugs, such as Demerol, Nisentil and codeine, the use of Nalline* is advised in conjunction with IPPB/I.[18, 19]

The pain resulting from chest trauma, frequently associated with one or more fractured ribs, inhibits breathing and especially coughing. An accumulation of secretions in the lungs results, and atelectasis of one or more segments may follow. Aspiration of secretions by means of a catheter introduced into the trachea is ineffective; at best it cleans the upper respiratory tract only. In this type of respiratory difficulty the use of IPPB/I may prove valuable. Treatment should be given

*Available from Merck and Company, Incorporated, Rahway, New Jersey.

repeatedly and over prolonged periods, but with a sufficient interval between treatments to allow the patient to recover from the tiring effects of mechanical breathing. During the intervals the patient may be able to expectorate the loosened secretions or may be effectively assisted in this by tracheal catheter aspiration. The use of Pancreatic Dornase in the nebulizer along with IPPB/I is recommended in the treatment of these patients.

Summary

A notation system for the growing, complex terminology currently employed in pressure breathing is suggested, the factors that enter into all types of pressure breathing — namely, timing, types and site of pressure applied — being taken into consideration.

A comparison is made of the various methods and equipment employed for pressure breathing employing face masks, hood-domes and body respiratory chambers, and their different physiologic responses are described.

The use of intermittent positive pressure breathing in the inspiratory phase of respiration (IPPB/I–Bennett) with the simultaneous administration of aerosols of bronchodilator drugs and in many cases Pancreatic Dornase (a polymerizing enzyme) was of considerable value in the treatment of 203 patients with a variety of disorders of the chest. Data on clinical effect as well as pulmonary function were tabulated, confirming this impression.

The favorable circulatory and respiratory physiologic effects of this form of pressure breathing are reviewed. An ideal type of pressure curve is recorded, demonstrating the pressure gradient exerted from the mouth down to the pleural space during inspiration and the rapid drop in pressure during the expiratory phase permitting a normal passive expiration. The flow sensitive features of the valve permit the patient with chronic pulmonary emphysema to exhale at will before starting a new inspiratory cycle.

We are indebted to Miss Dorothy Mellen and Miss Doris Grossman for technical assistance.

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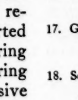

INTERSTITIAL-CELL TUMORS OF THE TESTIS IN CHILDREN

Report of a Case and Review of the Literature

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INTERSTITIAL-cell tumors of the testis constitute an interesting and relatively rare pathological entity. Tumors of the testis in themselves make up only from 0.5 to 2 per cent of all cancer in males, and the specific interstitial-cell tumor represents but 1 per cent of this total group.[1, 2]

During the past few years there have been several excellent reviews in the literature,[3-9] with a total of 46 cases reported to date. Of these, 13 have occurred in the prepubertal age group. The case reported below represents the fourteenth case occurring in a child.

NORMAL HISTOLOGY

Leydig, in 1850, first described the interstitial cells present in the stroma between the seminiferous tubules of the testis. The normal interstitial cell[9-11] is usually large (14 to 21 microns in diameter) and ovoid or polygonal in shape. The nucleus, which is round and pale and frequently eccentrically located, contains one or two nucleoli. Multinucleate cells are not uncommon. The cytoplasm is granular and fairly dense near the nucleus, but vacuolated peripherally. Various inclusions are present in the cytoplasm, which, in the fresh state, appears to be filled with highly refractile granules. These include numerous brownish lipoid granules (lipofuchsin) of varying size. Present at times are crystalloids, which are rod-shaped structures with round or pointed ends (Reinke's crystalloids). These are not seen until puberty, but persist thereafter.[12, 13]

The interstitial cells are usually collected in groups of four or five, in which small blood vessels are often present. The number of cells present varies in different persons at different periods of development. They are numerous in fetal life, probably owing to the influence of the maternal pituitary-like hormones during pregnancy, since the cells are actively stimulated by the luteinizing hormone of the anterior pituitary gland.[7, 14] At birth a marked reduction takes place, the cells being replaced by connective tissue. During puberty they begin to function actively in response to the gonadotropic hormones of the pituitary gland, and again increase in quantity, continuing to do so until maturity is reached, when the maximum amount is found. During adult life the cells gradually decrease in number.

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HORMONAL ASPECTS

The interstitial cells of the testis are believed to produce the androgen, testosterone, which is the male sex hormone. The cells function actively from boyhood to late middle life, elaborating their secretory product, which is distributed by the blood stream to exert its effect on various organs and tissues in the body. Testosterone stimulates the development and maintenance of the masculine sexual characteristics, such as enlargement of the external genitalia, deepening of the voice and promotion of distribution of facial and body hair in the male pattern. It also induces enlargement of the prostate and seminal vesicles and promotes the secretory activity of these structures.[7, 14]

Current methods for measuring testicular function are based on the fact that the testes secrete androgens. Androgens appear in the blood but in amounts too small to be demonstrated. Androgenic compounds are recovered from the urine of all normal persons, at any age, whether male or female. Minimal amounts are present in the prepubertal periods, but readily detectable quantities are found throughout adult life, declining gradually as senescence is approached.

It is generally agreed that the 17-ketosteroids of testicular origin are metabolites of androgen secreted by the interstitial cells. However, the urinary excretion of 17-ketosteroids appears not to be dependent on the activity of the testes alone, for the adrenal cortex is also an important source of androgen. Two groups of urinary 17-ketosteroids are recognized, an alpha and a beta component.[14, 15] Dehydroisoandrosterone, a major androgen of the beta component, is assumed to be derived solely as a metabolite of adrenocortical activity. The interstitial cells are accredited with producing the androgens that contribute to the excretion of the alpha 17-ketosteroids. Therefore, urinary steroid assays with determination of the different components are used as indicators of the interstitial-cell activity. Normal values of the average daily excretion of 17-ketosteroids in relation to age and sex have been established by Kenigsberg and his associates.[16]

Androgens produced by the testis have been found to be reduced in the castrate male, in eunuchoidism and in bilateral cryptorchidism, as well as in some patients with gynecomastia.[17, 18] Hypersecretion of testicular androgens results in an increased output of urinary 17-ketosteroids.

Although the androgenic steroids of testicular origin are accepted as being metabolites of interstitial-cell secretion, there has been no such agreement about the source of the testicular estrogens. Recently, however, Maddock et al.[19] presented conclusive studies attributing the elaboration of testicular estrogen exclusively to the interstitial cell. From their observations they concluded that the urinary estrogen excretion was a more accurate and reliable indicator of interstitial-cell function than 17-ketosteroid excretion, since the estrogens in men are mainly testicular in origin whereas both the testis and adrenal cortex are important sources of 17-ketosteroids.

Table 1. *Interstitial-Cell Tumors in Children.*

Author	Year	Age of Patient		Hair Distribution				Endocrine Changes
		When First Seen	At Onset	Chin	Chest	Axilla	Pubic	
		yr.	yr.					
Sacchi[21]	1895	9	5½	+	−	−	+	Macrogenitosomia
Rowlands & Nicholson[23]	1929	9	6	+	+	−	+	Macrogenitosomia
Sutherland[22]	1932	11	5	+	−	−	+	Macrogenitosomia
(Somerford[24])*	1941							
Stewart et al.[25]	1936	5	4	−	−	−	+	Macrogenitosomia
Huffman[26]	1941	6	4	−	+	−	+	Macrogenitosomia; gynecomastia.
Masson[13]	1941	9 yr., 7 mo.	4	−	+	+	+	Macrogenitosomia
Weiner et al.[27]	1942	6 yr., 9 mo.	5½	+	−	+	+	Macrogenitosomia
Rezek[28]	1943	10		−	+	+	+	Macrogenitosomia
Anderson[29]	1946	6		−	−	+	+	Macrogenitosomia
Melicow et al.[7]	1949	5	4½	−	−	+	+	Macrogenitosomia
Fraser[17]	1949	4	2	−	−	−	+	Macrogenitosomia
James & Shupe[30]	1950	14	9	−	−	−	+	Macrogenitosomia
Staubitz et al.[14]	1953	3	3	−	+	−	+	Macrogenitosomia
Pomer, Stiles & Graham	1953	7	6½	−	−	−	+	Macrogenitosomia

*Same case reported by Sutherland.[22]

Hyperplasia and Neoplasia

No definite criteria have been established for differentiation of hyperplastic states of interstitial cells from neoplasia, and thus much confusion has resulted. Warren and Olshausen[11] classified hyperplasia as "an increase of interstitial cells between the tubules without destruction or displacement of the tubules beyond the limits of the growth." In some cases hyperplasia has been so great as to simulate neoplasia. Neoplasia, to be defined as such, must have a localized tumor replacing or displacing the seminiferous tubules.[11] The criterion for cancer has been the presence of metastases,[13] although Warren and Olshausen[11] include among their criteria the demonstration of anaplasia and destruction of the tubules.

Hyperplasia usually occurs in testes reduced in size and therefore may merely represent a relative increase in cells. It is generally agreed that hyperplasia of interstitial cells occurs in any condition in which spermatogenesis is decreased.[5, 6, 11] Hyperplasia has followed vasectomy and compression or stricture of the spermatic cord and occurs in atrophic senile testes and in testes of patients with such chronic illnesses as tuberculosis, cancer, pernicious anemia and cirrhosis, as well as in some patients with acute illnesses. It may occur in any age group; associated endocrine disturbances are rare. Hyperplasia has also been made to occur experimentally through irradiation and administration of prolan, estrogens and triphenylene therapy.

Clinically, interstitial-cell tumors compose 1 per cent of all testicular tumors. Persons of all ages are affected, with extremes of four and eighty-two years. In adults the maximum incidence is between thirty and forty-five years of age. In children the onset tends to occur during the fourth and fifth years of life.[1, 8]

Interstitial-cell tumors of the testis are generally benign, but metastases have been reported[13, 20] and may occur years after removal of a primary tumor that appears histologically benign. Masson,[13] in reporting 2 cases as malignant tumors, commented on the considerable latent period between removal of the tumors and the appearance of metastases and indicated that other cases considered benign may be proved malignant after a sufficiently long follow-up period.

The endocrinologic manifestations are variable. In adults the tumor usually develops without any obvious endocrine disturbance, but with a loss of libido and production of gynecomastia in some cases. Testicular enlargement is usually gradual, and the tumor often goes unrecognized until it becomes sufficiently large to produce symptoms locally. In children these tumors all have been associated with precocious puberty, characterized by macrogenito-

somia, growth of pubic hair and deepening of the voice.

Precocious puberty caused by interstitial-cell tumors must be differentiated from various intracranial lesions, adrenocortical tumors or abnormalities causing hyperfunction of the adrenal cortex, and some familial or hereditary conditions that simulate precocious puberty. The diagnosis of intracranial lesions, such as tumors of the hypothalamus, pineal body and contiguous structures, and internal hydrocephalus is usually based on coexistent neurologic signs. Adrenocortical abnormalities produce associated laboratory findings in addition to precocious physical and sexual development. The diagnosis of interstitial-cell tumor is usually made through the palpation of a tumor in the testis in association with uncomplicated sexual precocity.

TABLE 1 (*Concluded*).

Side Involved	Color of Tumor	Friedman Reaction	17-Ketosteroids	Follow-up Findings
			mg. /24 hr.	
Left	Brownish			Regression of beard and voice; persistence of moustache; no change after 10 mo.
Left	Brownish			No regression 2 yr. after operation
Right	Reddish brown			No regression of secondary sexual characteristics 18 mo. after operation
Right	Brownish	Negative		Regression of hirsutism; no voice change 14 mo. after operation.
Left	Pale-gray-yellow	Negative		Genitalia smaller; no regression of pubic hair or breasts 2 yr. after operation.
Left	Dark brown			Metastases to liver
Left	Yellowish gray			Slight regression of secondary sexual characteristics; no change in voice 3½ mo. after operation.
Left			7.4, 10 (normal, 7-8)	No follow-up data available
Right	Yellow gray			Main symptoms regressed after operation
Right	Brownish	Negative		No regression after 6 mo.
Left	Rusty brown	Negative (Aschheim-Zondek)		Pubic hair practically disappeared; penis unchanged 5 mo. after operation.
Right	Light brown	Negative	9.8 (normal, 7.1-22.6)	No regression of precocious physical and sexual characteristics 9 mo. after operation.
Bilateral	Brown	Negative (Aschheim-Zondek)	39-73 before operation 113-162 after operation (Normal, 18)	Marked increase in 17 ketosteroids after operation with gradual decline; no regression sparing off of secondary characteristics.
Right	Deep tan		4.9 (normal, 3.8)	Penis unchanged; pubic hair less dense 2 mo. after operation.

Pathology

Grossly, the tumors are typically nodular and yellowish or yellowish brown, the color being due to the lipids present. The tumor may or may not be encapsulated, with fibrous tissue bands separating the tumor from the compressed testicular tissue. The size has varied from less than 2 cm. in diameter to the dimensions of a child's head.

Microscopically, the cells are large and polygonal in outline. They grow in sheets, cords and lobules, separated by intertwining collagenous stroma. Sometimes, columns of cells course along thin-walled vascular sinusoids. The cytoplasm is abundant and eosinophilic. It may be loaded with fine fat droplets. Intracytoplasmic lipofuchsin granules are commonly present whereas Reinke's crystalloids have not been found (Masson[13] states that they are never found in tumor cells). The nuclei are round, oval or wrinkled and contain one or more nucleoli. Mitoses are generally absent but may be present and abundant.

Case Report

R. O'R. (S. E. H. 53-4202), a 7-year-old boy, was admitted to the hospital on April 13, 1953. He had developed normally until 6 to 8 months before admission, when his parents first noted the development of pubic hair. At a later date this precocious development was noticed by a school physician, who advised endocrinological studies.

The past history was otherwise unremarkable except for a right inguinal herniorrhaphy performed at another hospital on January 10, 1948, because of an incarcerated indirect inguinal hernia. The operative note indicated that the operation was uncomplicated, with no involvement of testes or spermatic cord, and that convalescence was uneventful.

Physical examination revealed a well nourished boy, 56½ inches tall and weighing 76 pounds, who showed some advanced muscular development and appeared older than his stated age. The skin was soft and smooth. There was no abnormal pigmentation. No hair was observed in the axillas or on the face or chest. Pubic hair was present, and the penis was larger than normal for the stated age, measuring 8.0 cm. in length. A mass was present in the right scrotum (which was about twice the size of that to be expected in a 7-year-old boy) and was quite firm in consistence and nontender and did not transilluminate. The epididymis could not be differentiated from the testis. The left testis was normal in size and consistence. There was no gynecomastia. A well healed herniorrhaphy scar was present in the right inguinal region.

The temperature was 98.8°F., the pulse 88, and the respirations 20. The blood pressure was 114/70.

X-ray films of the skull demonstrated no intracranial calcification and no abnormalities of the sella turcica or pineal body. Chest films were normal. Urograms showed the left kidney to be somewhat lower in position than the right, but both kidneys had normal anatomic outlines and functioned well. There was no demonstrable adrenal enlargement or calcification. A soft-tissue film of the genitalia gave no evidence of calcification or abnormal changes.

The urine had an acid reaction and a specific gravity of 1.026 and was negative for albumin and sugar; no red blood cells, white blood cells or casts were present in the sediment. The hemoglobin was 15.5 gm. per 100 cc., and the hematocrit was 45 per cent; the white-cell count was 5800, with 68 per cent neutrophils, 30 per cent lymphocytes, 2 per cent eosinophils

and 242 circulating eosinophils per cubic millimeter fasting and 110 circulating eosinophils 4 hours after 0.3 cc. of epinephrine. The fasting blood sugar was 88 mg., the nonprotein nitrogen 23 mg., the calcium 10.8 mg., the phosphorus 3.1 mg., and the alkaline phosphatase 12.9 units per 100 cc. The chloride was 106.4 milliequiv. per liter. Urine 17-ketosteroids were 4.9 mg. per 24 hours (normal average for a child 5 to 12 years of age, 3.8 mg. per 24 hours). This value falls within the normal range for a 7-year-old child and is not significantly greater than the mean. The Friedman reaction was not determined preoperatively.

Orchidectomy was performed on the right on April 14. The postoperative course was uneventful.

On pathological examination* the gross specimen consisted of a testicle and epididymis enclosed in tunica vaginalis and

FIGURE 1. *Specimen After Sectioning, Showing Almost Complete Replacement of the Enlarged Testis by Pseudoencapsulated Tumor.*

attached cord, the latter measuring 5 by 1 cm. in the retracted state. The tunica albuginea was smooth and glistening, and no hydrocele sac was present. The epididymis was a discrete structure 4 mm. in greatest diameter. The testicle was almost round and was 2.5 cm. in diameter; on section it was replaced by a firm round mass, 2 cm. in diameter, that bulged up from surrounding tissue, giving an encapsulated appearance (Fig. 1).

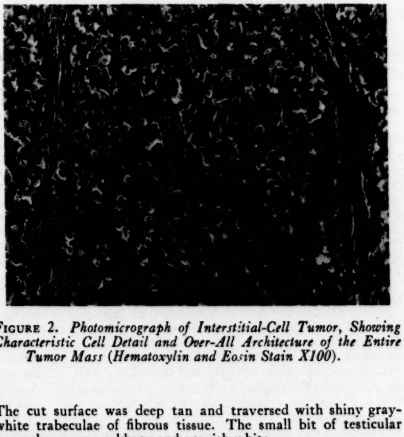

FIGURE 2. *Photomicrograph of Interstitial-Cell Tumor, Showing Characteristic Cell Detail and Over-All Architecture of the Entire Tumor Mass (Hematoxylin and Eosin Stain X100).*

The cut surface was deep tan and traversed with shiny gray-white trabeculae of fibrous tissue. The small bit of testicular parenchyma was rubbery and grayish white.

Microscopical examination disclosed large and round to oval, closely packed tumor cells, with distinct cytoplasmic membranes and centrally placed nuclei (Fig. 2). There were no mitotic figures. The nuclear chromatin was finely granular and evenly dispersed, and no more than one nucleolus was seen. The cytoplasm with hematoxylin and eosin stain was acidophilic and finely stippled; a few cells had a brownish granular material in the cytoplasm. No Reinke crystalloids were seen. With polychrome methylene blue and Masson's trichrome the cytoplasm had a finely vacuolated appearance, and with the latter a few deeply acidophilic round bodies were noted in the cytoplasm. Oil red-o stains showed finely granular, evenly dispersed red dots throughout the cytoplasm of most cells. Periodic-acid-Schiff stains were negative. The fibrous strands seen grossly were of dense collagen and supported large vessels. A few of these strands appeared invaded by the tumor cells. At the periphery the fibrous capsule was incomplete, for tumor cells grew out in tangential, finger-like fashion between testicular tubules, which were widely separated by edematous fibrous tissue. The tubular basement membranes were not thickened.

The diagnosis was interstitial-cell tumor of the testis.

The patient was discharged on April 20. At follow-up examination in June he was asymptomatic. The incision was healing well, and pubic hair had regrown, though not as densely as formerly. There was no regression in the size of the penis.

*E-53-1052.

DISCUSSION

Sacchi,[21] in 1895, presented the first case report of a tumor of this type occurring in a child exhibiting precocious sexual and physical development. Since then, a total of 13 cases have been reported. Table 1 summarizes the pertinent findings. In each case, except that reported by James and Shupe,[30] the pubertal changes began before six years of age; the patient described by James and Shupe was nine years old. Precocious muscular and skeletal development and macrogenitosomia have been common to all, and except for the case reported above, a voice change toward adult male tones has been characteristic.

There has been one report[15] of bilateral interstitial-cell tumors, all others being unilateral. The tumor present has been described as varying from pale grayish yellow to light, dark, reddish and rusty brown. The size has varied from 0.9 cm. in diameter to 12 by 10 cm. in greatest dimensions. Tumor weight has ranged up to 289 gm.

Friedman reactions and Aschheim–Zondek tests have been reported negative; determinations of 17-ketosteroids in the urine, which have been done in the cases most recently reported, have all been within normal limits, except that presented by Staubitz et al.,[15] in which an elevation to levels two or three times the normal values was reported; however, in this case the determinations were not performed until the patient had reached adult life, and comparisons with assays done in the prepubertal age groups may not be justified.

Masson[20] has reported the only proved case of malignant interstitial-cell tumor in childhood. Microscopically, this tumor showed no histologic characteristics that would have warranted the diagnosis of cancer or differentiated it from the other tumors reported, but follow-up studies revealed the presence of metastases to the liver. Therefore, an extremely long follow-up period seems to be necessary before one can classify these tumors as benign or malignant.

All the cases reported have been treated by orchidectomy. After the operation some of the secondary sexual characteristics have partly or completely regressed in most cases. The gynecomastia, present in only 1 case, failed to regress. All the patients retained their advanced skeletal and muscular development.

Summary and Conclusions

Thirteen cases of interstitial-cell tumors of the testis in children reported in the literature are reviewed. An additional case is reported. A brief discussion of the normal and abnormal histology, endocrinologic aspects and pathology of interstitial cells is presented. To date there are no definite criteria by which these tumors can be classified as benign or malignant, and a long follow-up period is essential.

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Since this paper was submitted for publication, another case has been reported.[31]

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ACTH AND CORTISONE IN THE TREATMENT OF KELOIDS*

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THE treatment of keloids, particularly old and large ones, has often been unsatisfactory. With the demonstration in recent years of the connective-tissue-inhibiting effect of ACTH and cortisone in laboratory animals and in human beings a trial in the management of keloids appeared justified.

We began their use in the first case of our series in December, 1951. A review of the literature shortly thereafter revealed two reports, both published in November, 1951, concerning the use of these steroid hormones in the treatment of keloids. The patient of Polson, Pattee and Woolhouse[1] was given cortisone intramuscularly in a dosage of 200 mg. daily for two days and thereafter 100 to 200 mg. daily. After eighteen days, during which he received a total of 2.75 gm., no change had been noted in the lesions. The keloids were then excised, and cortisone was continued in a dosage of 150 mg. daily, which was reduced to 100 mg. after four days. Sixteen days later oral administration of cortisone in the same daily dosage was substituted for the intramuscularly injected preparation. Twenty-five days after operation the patient reported that the scars were painful and itchy, as well as elevated and reddened, and that they were increasing in size. The dosage of cortisone was then increased to 200 mg. daily and the drug was continued at this level for another twenty days, at the end of which the keloids were obviously recurring; the authors noted that the time of recurrence was about the same as that experienced on previous occasions. They concluded that the total of 9.6 gm. of cortisone had no effect in preventing the recurrence of keloids in this case.

Conway and Stark[2] reported 2 cases in which keloids were removed surgically and ACTH was given during the postoperative period. In 1 case 60 mg. was administered daily for two days, followed by 40 mg. a day for the next twenty-one days. The other patient received 100 mg. daily for ten days. These patients had been followed for eight and five months respectively, with no recurrence. The authors treated 4 additional patients with intrakeloidal injections of a mixture of ACTH and hyaluronidase. In all 4 there was abatement or cessation of the symptoms of pain and itching, but in only 1 was there some change in physical appearance of the keloid.

More recently 2 additional reports concerning the management of keloids with these hormones have been presented. Goldman, Thompson and Trice[3] applied cortisone ointment to keloids, without prior surgery, and concluded that no effect was produced. De Kleine[4] used local cortisone injections for two patients. The keloid was excised, and the wound sutured, and this was followed by frequent injections of highly diluted cortisone (0.25 mg. per cubic centimeter) into the surrounding tissues during the healing phase and less frequent injections of undiluted commercial suspension (25 mg. per cubic centimeter) after healing was complete. The first patient, who received a total of 25 injections in five months, showed a complete recurrence within three months. The second received a total of 17 injections during a fourteen-week period; a limited degree of recurrence was observed. De Kleine concluded that this method offered little more than standard treatment with surgery and radiation. A recent editorial on hypertrophic scars and keloids[5] stated that clinical and laboratory trial of ACTH and cortisone was disappointing in that the hormones did not inhibit the development of these tumors.

CASE REPORTS

CASE 1. J. R., a 17-year-old Negress, had a bilateral mastoidectomy in 1940 at the age of 4 years. This was followed by keloid formation in each postauricular region. On examination in April, 1942, at the Tumor Clinic of the Rhode Island Hospital these measured 3.8 by 1.3 cm., with 0.7-cm. elevation. She was given x-ray therapy on 4 occasions, with no improvement. In July, 1943, both masses were excised, and the wounds closed by sutures. She failed to report for x-ray therapy after the operation. She was not seen again until April, 1945, when there was a keloid in each of the original sites. She did not report for further treatment until November, when another x-ray exposure was given, being repeated 1 month later. In October, 1947, an appendectomy was performed. She was rehospitalized in April, 1948, for a bilateral herniorrhaphy, and at that time it was noted that the keloids behind the ears were larger than before and that keloid was present in the site of the appendectomy incision. Seven months later keloid was present in the herniorrhaphy scars. In December, 1950, she began to complain of pain in the right postauricular area, and a discharge was observed emanating from the region between the keloid and the right ear where the skin had broken down. From December 22, 1950, to April 4, 1951, she was given injections of Kutapressin (a fractionated liver extract reported to be of value in the treatment of keloids[6]) in a dosage of 1 cc. subcutaneously. A total of 18 cc. was given, with no apparent change either subjectively or objectively. In February the left medial meniscus was removed after an injury to the knee. A keloid soon developed at the site of incision.

In December the patient was again seen at the Tumor Clinic complaining of considerable pain and discomfort from the postauricular keloids (Fig. 1*A* and 2*A*). On December 7, under local anesthesia, the keloid behind the left ear was removed with the electric cutting current, and the wound left open to heal by second intention. Twelve hours before the operation she was given 25 mg. of ACTH intramuscularly. Immediately after operation she was started on a course of ACTH in a dosage of 20 mg. every 6 hours. In addition an ointment containing 16.6 mg. of cortisone per gram of Aquaphor was applied daily to the granulating area.

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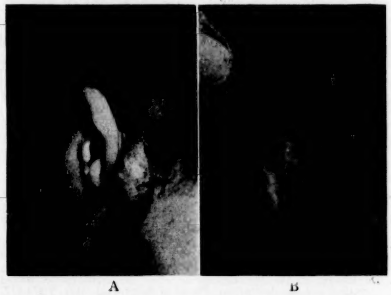
On December 13 the keloid behind the right ear was removed in the same manner, and the ointment was also applied to this site. ACTH was discontinued on December 18, after a total dose of 985 mg., and in its place cortisone was taken orally in a dosage of 25 mg. three times a day until February 20, 1952. The ointment was discontinued on February 13. The postoperative course was uneventful, the wounds gradually filling in and



A B

FIGURE 1. *Keloid in the Left Postauricular Region in Case 1 As It Appeared in December, 1951* (A), *and Appearance of the Same Area Seventeen Months after Combined Surgical and Hormonal Therapy* (B).

epithelizing. The patient was then seen periodically. On August 20 a flat, slightly elevated, linear mass with finger-like prolongations was observed in the right postauricular area; behind the left ear was a small area of thickening. Two months later the former mass was slightly larger, and the patient complained of itching in the area. On last examination, in May, 1953 (Fig. 1*B* and 2*B*), a small, oval tumor was present behind the left ear,

A B

FIGURE 2. *Keloid in the Right Postauricular Region in Case 1 in December, 1951* (A), *and Appearance of the Same Area Seventeen Months after Combined Surgical and Hormonal Therapy* (B).

and a linear, slightly elevated scar was noted in the right postauricular area. The keloids of the abdomen and knee are shown in Figure 3.

CASE 2. E. T., a 28-year-old woman, developed several keloids on the sternal region secondary to acneform pustules. These had been treated by x-rays and by operation, but had recurred each time.

On July 2, 1952, 2 keloids were excised, and the wounds sutured. Oral administration of cortisone, in a dosage of 25 mg. three times a day, was started on the day before operation and was continued for 3 weeks, with a total dose of 1.57 gm. In addition an ointment containing 16.6 mg. of cortisone per gram of Aquaphor was applied to the sites once daily for 1 month. On July 24 the patient reported the presence of considerable itching in the scars, and examination disclosed thickening and elevation of the left side of the upper scar. On August 7 she complained of pain and itching in the scars, and there was definite keloid formation in both. During the following 3 months

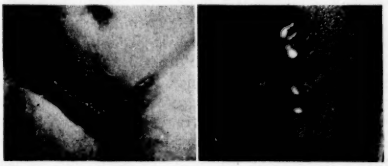


FIGURE 3. *Keloids of the Abdomen and Knee in Case 1 That Were Unchanged by Treatment with ACTH and Cortisone Alone.*

the keloids increased in size, and the symptoms became more severe.

CASE 3. A. K., a 22-year-old Negress, had her ears pierced at the age of 17. Six months later a lump appeared in each lobe, and itching began. The masses increased in size and were surgically removed, one in August and one in September, 1951. This was followed by radiation therapy. However, the lesions recurred in January, 1952. On examination on June 18 small keloids were present on the medial surface of each lobe, the one on the right measuring 1.6 by 0.9 cm., and that on the left 1.0 by 0.5 cm. On August 23 the keloids were surgically excised and allowed to heal by secondary intention. On the day of operation oral therapy with cortisone was started in a dosage of 25 mg. three times a day, and this was continued until September 25. She also applied an ointment containing 16.6 mg. of cortisone per gram of Aquaphor once a day until October 15. On September 17 a mass was palpated in the left ear lobe. One month later the medial aspect of the right lobe showed a recurrent keloid. On December 3 a mass could be palpated in each lobe, and keloids were present on the medial aspect of each.

CASE 4. E. N., a 14-year-old Negress, developed masses in each ear lobe at the sites of piercing. These gradually increased in size, but there were no symptoms of pain or itching. Examination on May 14, 1952, disclosed a large, firm mass measuring 1.0 by 1.0 by 1.5 cm. on the medial aspect of the left lobe and one measuring 0.5 by 0.5 cm. on its lateral aspect. The right lobe contained a firm, round mass measuring 5 mm. in diameter within its substance.

On May 28 the keloids on the left were removed by electrosurgery, large defects being left to fill in by granulation; the tumor on the right was removed with a scalpel, and the wound sutured. Because of a history of pulmonary tuberculosis cortisone was limited to local use. An ointment containing 16.6 mg. per gram of Aquaphor was applied to the operative sites three times a day for 2 months. On June 25 the lateral aspect of the right ear lobe showed a small lesion suggestive of a beginning keloid. On September 17 recurrence was noted on the left lobe. Two months later examination revealed thickening within both lobes and keloidal masses on the medial and lateral aspects of the left lobe.

CASE 5. S. G., an 11-year-old girl, received a laceration of the neck in July, 1951. She was seen 4 months later because of a large keloid, which had developed at the site of injury. During the following months she was given radiation therapy without effect. In March, 1952, the lesion was removed by electrodesiccation and allowed to heal by second intention. An ointment containing 5 mg. of cortisone per gram of neobase was applied twice a day. The patient was again seen 2 months later when the keloid had recurred and was approximately the same size as it had been before treatment.

Summary and Conclusions

The literature concerning the use of ACTH and cortisone in the treatment of keloids is reviewed.

Five cases treated with these hormones are reported. Each patient applied cortisone in an ointment base during the postoperative period. Three of these, in addition, received ACTH or cortisone, or both, by mouth or injection. In the 2 cases in which use of these hormones was limited to local application there was prompt recurrence. The keloid recurred in the other 3 patients as well. However, the retroauricular keloids of 1 patient were so small after therapy as compared to the original tumors that the result must be considered excellent. For want of any other explanation one must attribute the inhibition of recurrence to the systemically administered hormones. The keloids of abdomen and knee, which were not removed surgically, showed no improvement after hormonal therapy.

On the basis of this series of cases and reports in the literature it is concluded that cortisone and ACTH taken by mouth or injection without concomitant surgery are of no value in the treatment of keloids; cortisone ointment alone or in combination with surgery also appears to be without value.

Finally, systemically administered ACTH and cortisone when combined with surgery may be of value in some cases for the management of keloids. It is our opinion, however, that the treatment of choice is still surgery combined with radiation and that hormonal therapy, as described, should not be employed except in cases that have failed to respond to this method of treatment.

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MYCOSIS FUNGOIDES*

Report of a Case Terminating in Myelogenous Leukemia

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MYCOSIS fungoides (granuloma fungoides) is considered by many physicians to be a well recognized and distinctive, though uncommon, clinical and pathologic entity. Although at the time of its original description by French physicians in the early nineteenth century the disease was thought to be of mycotic origin, it has recently been properly classified as one of the group of lymphomas that affect the body.[1-5] Mycosis fungoides per se affects primarily the skin and in its late stages occasionally involves various internal organs, which show the same histologic changes present in cutaneous lesions. Also, more rarely, it may undergo transition and terminate in one of the other forms of lymphoma, such as Hodgkin's disease, lymphosarcoma or lymphatic leukemia. Even monocytic leukemia in its initial or aleukemic phases may mimic the clinical appearance of mycosis fungoides.[6, 7] The standard textbooks in dermatology as well as the various current articles about this disease stress the foregoing facts. Accordingly, the following case report is presented in some detail because of the varied and prolonged management of the disease, and its unusual type of fatal termination, which is believed to be unlike any previously reported case and also to be related to the prolonged radiation therapy that was given.

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Case Report

G. W. (M.G.H. 560360), a 46-year-old automobile mechanic, was first seen in the Skin Clinic, Out-Patient Department, in January, 1947. He complained of a generalized and pruritic eruption of about 20 years' duration and also of the appearance of large, raised, red lesions and ulcerations over the skin surface during the past 6 months.

The past and family histories were noncontributory.

Physical examination revealed that practically the entire cutaneous surface, excluding the face, was involved diffusely with scaly, infiltrated, erythematous patches throughout which were dispersed many discrete and confluent plaques, many of which had small central ulcerations and crusts. A large ulcerated lesion was present over the right lower abdomen. A few shotty inguinal and axillary lymph nodes were present, but the liver and spleen were not palpable. Blood counts and a urinalysis were normal, and a biopsy specimen taken from the skin revealed the typical pathologic changes of mycosis fungoides.

At this time low-voltage x-ray therapy was begun, being administered as a "spray" at weekly intervals to different body sections in a dose of 30 r unfiltered to each section (100 kilovolts, 10 milliamperes and target-skin distance of 61 cm. [24 in.]). This treatment was continued for 5 months, resulting in complete relief of pruritus and excellent, almost complete, clearing of the widespread dermatosis.

Six weeks later, however, because of a recrudescence of the skin lesions, urethane therapy was initiated. The patient received 1.0 to 2.0 gm. a day by mouth for 5 months, without any appreciable clinical change in his disease; indeed, skin lesions

continued to progress slowly and to become more widespread during this time. The hemocytologic picture remained normal throughout this period, and urethane therapy was finally discontinued because of the presence of a prolonged bleeding time (12 minutes).

In October, 1948, after a lapse of several months from observation in the Out-Patient Department, the patient was admitted for the first time to the dermatologic ward at the Massachusetts General Hospital complaining of increasing lack of strength and appetite, loss of weight, inability to work regularly and an increasing number of ulcerations and plaque formations of the skin. Laboratory studies, including blood counts, urinalysis, blood chemical determinations and a chest roentgenogram, were within normal limits. A skin biopsy specimen again showed the typical histologic features of mycosis fungoides.

On each successive day for 6 days 6.3 mg. of methyl-bis (beta-chloroethyl) amine hydrochloride (nitrogen mustard) was given via rapid intravenous infusion. This therapy resulted in a progressive and marked improvement clinically as evidenced by an increase in strength, weight and appetite, the healing of all ulcers by re-epithelialization and a regression and disappearance of many plaques and infiltrated patches. One month after entry to the hospital the patient was discharged in good condition and able to resume full employment.

In February, 1949, because of a continuing exacerbation of his skin disease he was readmitted to the hospital to receive a 2d course of chemotherapy. On this occasion 7.6 mg. of nitrogen mustard was given intravenously on each of 6 consecutive days, resulting, however, in only a minimal clinical improvement in pruritus and the healing of skin lesions. No abnormalities in the hemocytologic pattern were noted.

In March he was again referred to the Skin Tumor Clinic for resumption of superficial x-ray therapy. In general, fractional doses ranging from 30 to 180 r, unfiltered, were delivered at regular weekly or biweekly intervals either as a "spray" to different body sections or to individual, localized, active lesions. This therapy was carried out with few interruptions for a total period of 21 months (March, 1949, to November, 1950), during which the skin disease was well controlled and the patient remained in relatively good condition. Frequent checks of the peripheral blood pattern showed no abnormal changes, the white-cell count never falling below 6000 or the hemoglobin value below 14 gm. per 100 cc.

On November 27, 1950, the patient was readmitted to the hospital to receive ACTH, of which 200 mg. a day was given intramuscularly for 21 days, with no significant regression of the skin lesions but with considerable relief from the pruritus. A similar 21-day course of ACTH was given in January, 1951, with similar clinical results. No adverse effects of hormonal treatment appeared during either course, and, because of the lack of response to this therapy, he was again referred to the Skin Tumor Clinic for additional x-ray management. Interestingly enough, a skin biopsy specimen taken from the left leg at this time was reported by the pathologist as showing not only mycosis fungoides but also radiation changes in the corium.

Thus, for another period of 9 months, from March to December, 1951, he continued to received regular weekly or biweekly x-ray treatments in doses ranging from 45 to 300 r unfiltered. During the latter half of this period, however, the development of a progressive anemia and leukocytosis was noted and, concomitantly, he gradually experienced an easy fatigability, generalized weakness, loss of energy, strength and appetite, and nocturnal ankle edema. Therefore, in January, 1952, he was again admitted to the hospital for the fifth and last time for further study and treatment. It was calculated that over the preceding 5-year period he had received in fractional doses the accumulated sum of 24,630 r unfiltered of superficial, low-voltage x-rays to the entire skin surface. The individual area totals are shown in Table 1.

Physical examination revealed a chronically ill and moderately wasted man. The skin in general was thin and appeared atrophic and darkly pigmented, with irregular islands of depigmentation scattered throughout its surface. In addition red, scaly plaques, purplish-red nodules and tumors and crusted, secondarily infected ulcerations were present diffusely. There was a complete alopecia of the scalp and an ectropion was present over the right lower eyelid. The heart and lungs were normal, except for an apical rate of 108 and a Grade 2 precordial systolic murmur. The liver and spleen were not palpable. There was a ++ pitting ankle edema bilaterally and also generalized, shotty lymphadenopathy.

Examination of the blood showed a hemoglobin of 9.5 gm. per 100 cc. and a hematocrit of 32 vol. per cent. The white-cell count was 15,800, with 26 per cent neutrophils, 32 per cent lymphocytes, 2 per cent monocytes, 26 per cent eosinophils, 4 per cent basophils, 6 per cent myelocytes, and 4 per cent myeloblasts. Platelets were abundant. Urinalysis was negative. The nonprotein nitrogen was 29 mg. per 100 cc. The total protein was 7.70 gm. per 100 cc., with an albumin of 3.53 and a globulin of 4.17 gm. (albumin-globulin ratio of 0.8). A chest roentgenogram demonstrated no abnormalities in the heart, lungs or mediastinum, and a plain film of the abdomen disclosed no enlargement of the liver or spleen. Bone-marrow preparations revealed a marked shift to the left in the myeloid series, with a myeloid-erythroid ratio of 9:1. Megakaryocytes were abundant. Blast and early forms were also noted in the peripheral blood smear, and these changes were regarded as consistent with early myelogenous leukemia.

The patient progressively failed in spite of multiple blood transfusions (13), a 4-day course of nitrogen mustard, cortisone, penicillin and streptomycin. The white-cell count continued to rise steadily, finally reaching a peak of over 115,000 2 days before death, with an associated severe neutropenia and thrombocytopenia. Terminally, a bilateral lobar pneumonia developed and multiple spontaneous hemorrhages occurred in the skin and mucous membranes. The patient quietly died in coma on the 80th day of hospitalization. A differential blood count performed 1 week before death showed the following pattern: 8 per cent myeloblasts, 60 per cent promyelocytes, 8 per cent myelocytes, 10 per cent metamyelocytes, 10 per cent neutrophils, 2 per cent eosinophils and 2 per cent lymphocytes. Platelets were absent from the smear.

TABLE 1. *Amounts of Unfiltered, Low-Voltage Radiation Delivered to Various Skin Surfaces.*

SURFACE	X-RAY DOSAGE r
Anterior and posterior parts of body	7320*
Right and left lateral parts of body	6390*
Upper and middle back	960
Entire face (all sides)	1020
Anterior part of chest	480
Lateral thorax (each side)	420
Scalp area	840
Forearms (extensor and flexor surfaces)	1260
Abdomen	600
Anterior and medial portions of thighs	600
Buttocks and posterior portions of thighs	1020
Lower legs	840
Feet (soles, sides and dorsa)	2880
Total	24,630

*Delivered as "spray" radiation.

At post-mortem examination* the final anatomic diagnoses were as follows: mycosis fungoides; myelogenous leukemia, chronic, with infiltration of lungs, liver, spleen, kidneys and lymph nodes; bronchopneumonia, severe, with microabscess formation; pulmonary edema, massive; organizing pneumonitis, focal; splenic infarcts, multiple; pleuritis, healed, bilateral; coronary sclerosis, slight; and adrenal necrosis, unilateral (?secondary to leukemic infiltration).

DISCUSSION

Most dermatologists and pathologists agree that true mycosis fungoides shows no specific bone-marrow changes. Tilley and Smith[8] recently re-emphasized this point, having examined the bone marrow in 6 patients with this disease and finding no evidence of leukemia. In 3 patients of their group several observations were made throughout the course of the illness. I have personally observed 5 other proved cases of mycosis fungoides in the past four years without evidence of leukemia either by ante-mortem examination (peripheral blood

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cells, lymph node biopsy and bone-marrow aspiration) or at autopsy; 1 patient in this group died with a severe aplastic anemia after generalized cathode-ray irradiation.

The hematopoietic depressant action of x-rays is also well known. Pascher and Kanee[9] studied the hemocytologic pattern in 8 patients with generalized dermatoses of various types, 4 of whom had mycosis fungoides, who were treated with low-voltage x-rays. Leukopenia was consistently produced in these patients, and hypochromic anemia also developed in some of the group. The authors concluded that low-voltage x-rays are harmful to the hematopoietic tissues of radiosensitive patients. MacKee and Cipollaro,[10] in their standard textbook, also thoroughly discuss these bone-marrow effects; in addition, they mention the possibility of leukemia after prolonged irradiation over parts of the hemopoietic system — the long bones, spleen and so forth. Lynch,[11] moreover, records a case of death from acute myelogenous leukemia associated with extensive chronic radiodermatitis in a patient who had received numerous x-ray treatments for a generalized psoriasis over a twenty-five-year period. Also, it is common knowledge that the various types of leukemia occur more frequently among physicians (and other persons) who are repeatedly exposed to various ionizing radiations than among other groups of physicians not exposed regularly to the same emanations.[12]

The nitrogen mustards also frequently exert a cytotoxic action on the hematopoietic system when used in therapeutic doses in cases of mycosis fungoides. In 4 of 6 such patients treated with nitrogen mustard by Henstell et al.[13] lymphopenia, neutropenia, thrombocytopenia and moderate anemia were noted. Interestingly enough, Gilman and Philips,[14] in an analysis of the biologic actions of the nitrogen mustards, present evidence that these chemical agents have a primary nucleotoxic effect in susceptible cells. Inhibition of mitosis, shrinkage and fragmentation of chromosomes and ultimate destruction of the cell nucleus (and the cell itself) followed heavy doses of these chemicals. Treated cells that recovered from a mild dose of nitrogen mustard frequently transmitted chromosome abnormalities to daughter cells for several succeeding generations before a normal nuclear appearance returned. Observations were made on several different kinds of biologic material. It was further noted that these nuclear effects resemble most closely the action of x-rays on cells rather than that of any known chemical reaction.

From the case reported above it will be noted that the patient received three distinct and separate courses of generalized irradiation for his skin disease over the five-year period between January, 1947, and January, 1952. The first course, which lasted for five months during the early part of 1947, resulted in an excellent and complete, though temporary, regression of all cutaneous lesions. The second course was carried out over a twenty-one month period between March, 1949, and November, 1950, during which the disease was controlled reasonably well and the bulk of the total amount of radiation was delivered to the skin surface. This second period of x-ray therapy had been preceded by two courses of nitrogen mustard, the first with excellent, though again temporary, results and the second with only partial benefits.

The third course of generalized radiation therapy covered a nine-month period in 1951 during the latter half of which the symptoms and signs of leukemia developed. This occurred approximately a year after the extensive and prolonged second course of therapy. The large amounts of superficial x-rays administered, and the intervals involved for the development of leukemia, together with present clinical knowledge regarding the injurious effects of x-rays on human tissues, appear to be good evidence that the myelogenous leukemia in this case developed as a complication of low-voltage, generalized irradiation. Whether or not nitrogen mustard can be considered to have had an enhancing effect in this process remains speculative.

Summary

A case of mycosis fungoides terminating fatally in myelogenous leukemia is presented.

It is suggested that the leukemia developed as a sequel to the large amounts of superficial, generalized x-ray therapy administered in this case.

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SPECIAL ARTICLE

REFLECTIONS ON POSTGRADUATE MEDICAL EDUCATION FOR PRACTICING PHYSICIANS

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BOSTON

THE continuing professional education of practicing physicians constitutes one of the most important, difficult and neglected problems facing American medicine today. It is unnecessary to labor the point that the complexity and rapidity of developments in all branches of medical knowledge have forced the modern physician to be continually going to school if he is to be considered competent and well trained. It is no longer sufficient for a man to have a background of study in a good medical school and as an intern and resident. Granted, therefore, that the doctor needs retraining, a corollary is that the general practitioner in the country needs this retraining most of all. This is true because of the wide scope of his practice, which often embraces, of necessity, specialties with which the urban practitioner does not concern himself, and because of his relative isolation from contacts with his medical fellows. The problem of providing adequate opportunities for medical education of these doctors is the most difficult. Undoubtedly, one of the great deterrents to entering country practice has been this failure to provide proper means for keeping up to date. A solution would go a great way toward maintaining medical practice at a high standard in the rural areas and also in easing maldistribution of physicians between the country and the city.

In view of these facts it is surprising how little attention the problem has received. Neither the proponents of "individual enterprise" nor the advocates of socialized medicine have much to say about this cardinal requirement for providing good medicine. Medical schools, so much bedeviled by their own economics, have, with few exceptions, hesitated to branch into a field that might entail a drain on their overburdened exchequers. Foundations have provided millions for research but have done relatively little about the weak link in the chain between producer and ultimate consumer. Of what use is all the knowledge building up in the laboratories if its practical fruits, the proper technics of application, are not being taught?

Of course, there are groups that are alive to the importance of this subject and are doing something about it. One is the American Academy of General Practice. Also, many state societies have programs of medical education, and among these the Massachusetts Medical Society has been in the forefront for years. For the most part, however, their expenditures in this field have been a pitifully small part of their budgets, and their programs have been haphazard.

There is always a danger when restricted or special-interest groups concern themselves with education that their educational activities will be subordinated to other objectives of the organization — the professional status of its members, legislation, lay education or fund raising — or will be slanted by these objectives. This applies in varying degrees to colleges, academies, special societies, state public-health departments and voluntary health organizations. Thus, many special societies set up qualifications for admission, and many are concerned with boards of certification, but once having admitted a man to membership, they seem to have little interest in the speed with which he deteriorates. Unlike most societies the American Academy of General Practice requires recurrent medical refreshment for continuing membership.

Many a physician will take issue with some of these remarks regarding the inadequacy of educational opportunities. Particularly if he lives near a medical center he will complain of the number of medical meetings he should attend — hospital-staff and society meetings for the most part. They all provide some tidbit of medical information in the form of a lecture or a clinic. Seldom, however, is an over-all program planned with a view toward the real needs of practitioners, and never is there co-ordination between various groups in program planning.

A situation has developed that is not altogether wholesome. The groups interested in teaching doctors are not co-ordinated, and teaching is not in the hands of professional educators. The professional educators for the most part stand on the sidelines, bemoaning the fact that the amateurs have taken over, but not yet ready to offer a dynamic plan of their own.

Nor can doctors get the instruction that they need from the numerous medical journals. No practicing physician has time to sift through the mass of data for the kinds of helpful knowledge he wants, and few have the background and training to judge the value of the scientific presentations. Survey articles, such as the Medical Progress reports in the *New England Journal of Medicine*, are helpful, but too often their chief objective appears to be a demonstration of the author's wide acquain-

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tance with the bibliography of the subject rather than a critical attempt to winnow the wheat from the chaff. By far the most handsomely printed and often the most readable are brochures published by many of the larger pharmaceutical houses. Although the interest of these concerns in the education of physicians is commendable more effective instruction might result if the money expended in this way were pooled to set up a fund for the development of a real program of postgraduate education.

The character of most instruction also leaves much to be desired. My great uncle attended Harvard Medical School by purchasing a series of course tickets for lectures on pharmacology, materia medica and so forth. Educators shudder at the quality of that type of undergraduate instruction today, when bedside teaching and learning by doing are the order of things. But how does the modern general practitioner get his instruction? — by lectures, usually poorly delivered, at a time of day when both he and the lecturer are nodding with fatigue. Why is the type of instruction that was outmoded fifty years ago for medical students the best for the physician in practice? The answer is that it is not but that postgraduate education is fifty years behind the times.

At present the best modern physician education is obtained by daily attendance at a large modern teaching hospital with exposure to the stimulus of eager residents and medical students in discussions at the bedside of well studied patients, and by intimate and informal contact with many specialists in various fields at conferences, at the luncheon table and in the hospital corridors. Those fortunate enough to have this kind of teaching frequently do not appreciate it, it is so much a part of their medical lives. It cannot fully be attained except in limited areas. But this goal can be aimed for everywhere, and it has been demonstrated in many comparatively rural areas that it can be reached.

In the first place education should be part of the daily life of the physician, not a special event like a holiday. Therefore, it must be brought to him. My admiration is unbounded for the numerous doctors who sacrifice precious time and energy to make weekly pilgrimages in the dead of winter and at unearthly hours to attend meetings and courses at teaching centers that may be as far as 100 miles from their homes. But many of their colleagues do not have such initiative, and they themselves cannot repeat it too frequently. Nor are full-time courses lasting weeks to months at medical centers the answer: they serve a function in the intensive instruction in a special field of a medical technic, but they have only limited applicability for teaching general medicine, since the courses must be so long — at least three months — to have any value that few can afford the time and money to take them.

The best way of bringing medical teaching to the doctor's own doorstep is to develop in the community hospital an approximation of the teaching hospital. This means at a minimum that these hospitals must have adequate ancillary services such as laboratory and x-ray facilities and that the staff must be so composed that the best qualified men have posts of responsibility and morale is high. The medical resident is undoubtedly the kingpin in this type of teaching; he is thoroughly familiar with the cases to be presented and occupies a neutral position since he is not directly in competition with the staff members, and, because he is junior to them, his remarks can be discussed with freedom. These requirements have been well appreciated by several groups concerned with teaching problems, such as the Bingham Associates at Tufts College Medical School and the Rochester, New York, plan.

The problem of the resident in these hospitals has been the most difficult aspect in the development of this type of teaching program since it has proved impossible to obtain enough mature, well trained residents to serve in hospitals of this type. Although every effort should be made to set up an effective resident system, often through affiliation with university teaching hospitals, postgraduate education cannot wait for this. An effective program can be established without residents. Its success depends on one or two key men who are energetic and imaginative and who are respected by their colleagues. Sessions should be held regularly and should be of the grand-rounds type of exercise with actual case presentations, which should be concise and to the point, with an interpretation by one or more consultants, followed by open discussion. The consultants may be either local or imported. One advantage of the imported consultant is that he is not in direct competition with other members of the staff as local men usually are, and hence the exchange in discussion is freer. When there are several hospitals in close proximity the development of a co-ordinated program is logical and efficient but is not often done.

This type of program has incidental effects that should be of vast benefit to the local medical community. It is a great stimulus to the establishment of the regional hospital as the hub around which the medical practice in each area rotates. This it accomplishes by helping to maintain and even raise medical standards, giving the community a sense of pride and accomplishment and making it a more attractive place in which to settle and practice. When co-ordinated programs are established between hospitals the neutral ground of these programs brings together groups from different hospitals within the city or between neighboring towns, which are sometimes divided by factional differences.

Postgraduate education cannot wait until every community hospital in the state acquires the tangible and intangible attributes to make it the vital

center of the teaching program. Therefore, programs of a different type must be set up until these centers can be locally developed and for physicians who for one reason or another do not live in areas that lend themselves to community hospital programs. There have been many circuit-rider programs carried on in Massachusetts and elsewhere. Most of them employ the lecture system and suffer from the defects of this type of presentation. It is far better to aim at the informal clinical conference presentation, with panels of two or more instructors who will lead the discussion informally. The free exchange of such discussions tends to foster increasing participation by the audience. Various points of view can be presented and defended; problems can be reiterated and clarified, and the subjects of most interest to the listeners brought out. The psychologic effect of varying voices and opinions in this panel type of communication tends to keep the audience interested and attentive throughout the session.

Preliminary planning and arranging is essential to the continued success of this type of program, which can easily be spoiled by lack of attention to details. On more than one occasion I have driven 50 miles or more to give a talk scheduled for 8:15 p.m. only to find that I was the only person in the hall except perhaps the chairman, who informed me that "of course no one gets here before nine because of office hours." Or there was no projector, or the cases to be presented were not there, or the presentation took up half the time. And the audiences have as much to complain of: the speaker arrives late, does not show up, is ill prepared or gives some warmed-over paper on a technical subject of no general interest. Such planning, which requires experience and attention to detail, before, during and after the exercise, can best be carried out through a central organization.

The lack of competence of most physicians as speakers is not surprising. After all, they spend their time doctoring and not orating. Medical teachers need not be orators but they can avail themselves of some of the modern visual aids in teaching and learn some of the rudiments of clear presentation. Too often slides used are so complicated that they merely confuse. Medical movies, colored slides and so forth have great value as adjuncts in teaching. Much assistance in the planning and execution of teaching exercises can be given by a professional organization.

How can physicians be persuaded to avail themselves of the opportunity offered? Doctors are busy men, and it entails sacrifice and energy to spend much time on postgraduate training. Some doctors are motivated by the real desire to keep abreast of things and to continue to be well trained; they will take advantage of the opportunity. Many others (often those who need instruction the most) are much more laggard and have to be prodded. Providing the educational opportunities on their home ground is helpful since it makes it easier for all to attend. Furthermore, patterns of professional behavior tend to be set up that are catching since most human beings are by nature conformists. What other incentives are there? The patients themselves are demanding and receiving medical knowledge more and more. It behooves the medical profession to be aware of this and to see that this craving is satisfied in a sound fashion and not by sensational, pseudoscientific reporting.

Adequate postgraduate teaching cannot be obtained without some cost. How is it to be paid for? The medical schools are already too hard pressed to be expected to contribute financially, however greatly they can assist in planning curricula and providing trained instructors. Foundations may give some help but mainly on a pump-priming basis. Medical societies certainly should recognize the maintenance of the standards of their members as a major function and support their programs accordingly. Hospitals should support them for the same reason. A cardinal part of the programs of many of the larger health organizations is physician education. Such organizations might well consider the advantages in efficiency and economy of channeling their work along these lines through a central planning group. The remainder of the support will come from those who directly benefit — the participating physicians themselves. A modest fee is reasonable if the medical teaching is good. Most physicians are opposed to hand-outs.

The Postgraduate Medical Institute recently established in Massachusetts was designed to carry out these objectives under the sponsorship of and with support from the Massachusetts Medical Society. It will co-ordinate the activities of all agencies concerned with postgraduate education, and in particular it will call in the expert help of the medical schools in the Commonwealth. It will conduct courses, carefully planned for the needs of practicing physicians, but it will in no way interfere or compete with the teaching activities of established groups that wish to carry on their own programs. It is prepared to offer assistance to community hospitals or similar groups that wish to develop local programs. Finally, it will be in a position to experiment with and find various new technics of teaching in this most difficult of fields.

MEDICAL PROGRESS

DERMATOLOGIC RESEARCH*

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PHILADELPHIA

DERMATOLOGIC research has become a rewarding and exciting venture for an increasingly large band of investigators. Uniquely available, the skin offers a rich variety of problems susceptible to attack by all the basic methodology of medical research. A single hair, a drop of sweat, the invisible film of sebum — each offers a stimulating challenge to investigators. Here are frontiers of exploration at one's very finger tips.

The skin is no mere phase boundary. It is an immense fabric with a functional patterning, designed for the best protection of the man within. In every portion one can read the magnificence of this protective design: the epidermis, manifesting a high state of physical as well as chemical impermeability; the melanocyte, elaborating the sun screen, melanin; the sweat gland, providing evaporative cooling; the vascular channels, facilitating radiant heat transfer; and, finally, the vast neural system, giving information of every impending physical change that might herald danger. And here and there are vestigial traces of an evolutionary climb: the "goose flesh," which in the furred mammalia gave added thermal guard, the apocrine glands, which in lower forms produce a scent to discourage attack, and the toe and finger nails, suggestive of reptilian armor plates.

Fundamentally, the skin and its appendages are units that permit internal homeostasis, and, as such, their operation and maintenance have interested men from every branch of medicine. Recent examples of such interest in the skin are numerous. The internist has given attention to the chemistry of the sweat gland as an index of the levels of the steroid hormones.[1] Surgical interest has concerned the role of the circulatory responses of the skin in shock states.[2] The anatomist, in a trend toward histochemical description, is carefully scrutinizing the microanatomy of the skin.[3] The microbiologist is assessing its remarkable disinfectant properties.[4] Physiologic chemists are actively investigating the relation of enzymes to the skin.[5] Pharmacologists are now concerned with the action of sympatholytic agents on cutaneous vascular responses.[6] The physiologist, with a special, century-old interest in the sweat glands, has encompassed a wide range of studies on the function of the skin.[7] Finally, the pathologist has found the skin as the nearly perfect vehicle for his adventures in experimental carcinogenesis.[8]

But to turn to the men at the center of dermatologic research, this review has been planned to present the current trends and directions of the dermatologists. Here, no departmental barriers obstruct the approach. The dermatologic investigator utilizes the tools, technics and theories designed to answer the question best. Thus, in studies on pigmentation, approaches range from physiologic through histologic to chemical and biophysical.

In this review the task is one of selection. I have chosen to survey some phases of dermatologic research in which definite, co-ordinated advances appear to have been made during the last few years. Purely clinical studies are not considered, although a single example of how investigations from widely separate fields have disclosed the true nature of a clinical problem is presented at the close of this report.

Skin is heterogeneous. Actually, it invests the body in an inner connective-tissue sheath, containing collagen, reticulin and elastin, and in an outer epithelial or cellular layer. Distributed over the entire skin surface are the invaginations of epithelium that have achieved cellular specialization in the production of water, oil and protein — for example, the sweat glands, the sebaceous glands and the hair follicles.

The cellular layer, or epidermis, and its specific appendages are the subject of this review.

KERATIN

Nowhere can the cycle of age be seen better than in the epidermis. Here billions of cells are aligned in less than a dozen rows that accurately reflect as many stages in their month-long life. The youngest cells in the lowest band are gradually pushed outward by new division arrivals. During this progression toward death dramatic changes in morphology can be seen. The cells begin to present a granular cytoplasm, the intercellular connections become lost, cellular details fade, the nuclei disintegrate, and finally the cells die and become indistinguishable. A thin sheet of amorphous organic material remains. Chemical analyses reveal that this is largely composed of one of the most resistant and chemically inert of all biologic compounds. It is a scleroprotein, keratin. The name derived from the Greek Keras, or horn, gives a clue to its physiologic role of protection. Keratin is the

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outermost fringe, a perimeter deceptively effective. It is defense in depth against much of the microbiologic flora; it provides more than token resistance to organic as well as inorganic chemicals, and it insulates against heat and light rays. But for this chemically inert boundary all human beings would be subject to a constant etching by their environment.

Although intimately woven to a perfect fit, it is still elastic to the point of physiologic adaptation to sudden changes in volume.

The chemistry and the histogenesis of keratin have been widely studied.[9] With few exceptions each epidermal cell gives its life to the formation of this protein. In the young, metabolically active cell the proteins are living globular structures. Rapidly, during the few weeks of its life, the cell converts these to dead rods of keratin. All this involves oxidation and dehydration.

The chemistry of keratin merits closer examination. Like all proteins it is composed of numerous parallel chains of polypeptides, which in turn result from the linkage of amino acids. Keratin has a unique distribution of three amino acids (arginine, lysine and histidine), which are basic rather than neutral in their chemical binding properties. It also has a high content of sulfur that reflects the presence of the amino acid, cystine. Keratin, according to some methods, has a molecular weight of 160,000, which is in keeping with its protein nature. It is birefringent — that is, because of its fibrous structure, it will rotate polarized light to produce optical changes. It has a strong affinity for both basic and acidic dyes. It is insoluble in dilute acids, alkalies, water and organic solvents. Moreover, the enzymes, trypsin and pepsin, are ineffective against it. All in all, keratin is an extremely resistant compound.

Little is known regarding the chemistry of keratinization. It is possible, however, to outline broadly the nature of this process. During keratinization, the sulfhydryl groups of the living epidermal cells are oxidized to disulfide groups; in other words, the shift is from cysteine to cystine. This change is accompanied by a loss of water and results in stable sulfur linkage in the keratin molecule. Additional hydrogen bonds or bridges are known to exist, and these provide electrostatic linkage forms. The loss of water during keratinization is to be compared with the drop in water content in the epidermis. The lower levels can be shown to contain 70 per cent water, whereas the stratum corneum, essentially keratin, may contain only 10 per cent.

From the physical standpoint keratin is hygroscopic, and accordingly the hydration of the stratum corneum reflects in part that of the circumambient air. In the dry cold of winter the keratin is correspondingly dry and is actually brittle; the clinical concomitant being "chapping" due to disruption of the keratinous protective layer. Such keratin dehydration is minimized by an adequate coating of the stratum corneum with sebum that retards rapid aqueous exchanges.

Emphasis has been placed on the chemical inertness and indestructibility of keratin. However, there are two major methods of degradation of keratin, either the disulfide or the hydrogen bands being attacked. In the first process any strong reducing agent may be employed. It is simply a shift in reverse of keratinization (this is the basis of all "cold-wave sets" used in the popular permanent-wave technics). Arrested at the proper stage and reoxidized, the keratin may regain most of the former tensile strength, and yet may show a new molecular configuration. In the second method of keratolysis the hydrogen linkages are disrupted by the action of such chemicals as phenol, resorcinol, salicylic acid and hydroquinone.

The popular detergents have brought havoc to the grease of housewives, "pots and hands." But more than this, Van Scott and Lyon[10] have detected a keratolytic action of the detergents. They have shown that incubation of various types of keratin in detergent solutions leads to an increase in the measurable sulfhydryl group level. This is indicative of a denaturing effect on the keratin molecule, although the precise mechanism is as yet not apparent.

Nails and hair also present a keratin structure. Furthermore, it is of considerable interest that a keratin forms the organic fibrils that surround the inorganic crystals of the enamel of the teeth. The enamel is truly a super skin produced by epithelial cells, to defend the teeth from, among other things, the invasive attacks of micro-organisms.

Melanin

In the twilight of fetal growth a migration of special cells occurs from the neural crest out to the epidermis. These cells soon become permanent residents of the epidermal community and concern themselves with the elaboration of a protective black pigment. This pigment is known as melanin, and the cell as a melanocyte. Thus, two separate important metabolic functions occur in the outer layer of skin. Each is influenced by a specific group of morphologically distinguishable cells — keratinization, as described above, is achieved in the classic epidermal malpighian cell; melanin formation takes place in the neural immigrant cell, the melanocyte. A tremendous amount of research effort has been expended in the study of melanin, and it is possible to present satisfying general concepts in this field.[11]

The melanocyte has the distinctive anatomic imprint of its neural origin. It is readily distinguished in the basal layer of the epidermis by its long dendritic cellular branches. Moreover, it lacks the tonofibrils or intercellular bridges of the true epidermal cell. These tubular neural branches

of the melanocyte ramify between the malpighian cells and often end in characteristic caps. Many of these cells are pigmented, being loaded throughout with melanin granules; the majority show darkening on incubation with dihydroxy-phenylalanine (dopa test). The cells show a series of morphologic variations in correlation with activity and age. As a result, a large number of names arose when observers initially believed they were viewing a variety of cell types. However, Billingham and Medawar[12] have convincingly classed all branched epidermal cells in one morphologic lineage. Thus, the clear cell, dendritic cell, melanoblast, dopa-positive cell, Langerhans cell and melanodendrocyte are all synonyms for the melanocyte.

The melanocyte is the cellular site for the manufacture of melanin. In its absence, as in albino skin, pigment is not formed. The activity and number of these melanocytes determine the epidermal color. The duration of the life cycle of melanocytes is unknown, but eventually these cells age and join the general outward flow of moribund epidermal cells to be cast off at the skin surface. As they age they appear higher in the epidermis and show some changes in staining. It is then that they appear in gold-impregnated sections as the Langerhans cell.

Basically, the intimate cellular chemical changes occurring during the formation of melanin can be represented as follows:

Tyrosine ⟶ Dihydroxyphenylalanine ⟶ (Intermediates) ⟶ Melanin

The entire conversion appears to be catalyzed by a single enzyme, tyrosinase, formerly labeled dopa-oxidase. It is interesting that for fifty years the melanocyte has been functionally identified as the epidermal cell that darkened in vitro in the presence of a substrate of dopa. Actually, it can now be shown that the amino acid, tyrosine, rather than dopa is the primary substance in melanin formation.

The end product, melanin, is a relatively insoluble substance of high molecular weight. It results from a polymerization of the oxidation products of dihydroxyphenyl compounds. Under the electron microscope melanin granules may be seen as regular spheroid particles, and not simply as precipitated aggregates.

Because of the opportunity of studying melanin formation under in vitro conditions a vast fund of information is available on the agents that affect the synthesis of melanin. Substances such as glutathione, cysteine and BAL, which combine with copper, are inhibitory. Also, derivatives of tyrosine are effective inhibitors since they act as competitive substrates. Another example is the hydroquinone group, which acts partly as a reducing group. Conversely, ultraviolet light and an increase in temperature promote melanin deposition. From the nutritional standpoint vitamin deficiencies may either decrease or increase pigmentation. Lack of the vitamin B complex has been associated with depigmentation, whereas hyperpigmentation has been seen in vitamin C deficiency. Copper, furthermore, is essential at least in trace amounts, since it represents part of the tyrosinase moiety. Hormonal factors are of significance, the sex hormones being responsible for selective pigmentary changes — for example, in the linea alba and about the nipples. The hyperpigmentation of Addison's disease is as yet incompletely explained. Recently, it has been shown that a pituitary-melanocyte-stimulating hormone is increased in these patients, with a subsequent increase in melanocyte activity. Neurogenic factors in pigmentation are recognized but as yet not completely understood.

Hair

In man hair is a rudimentary vestigial skin appendage. Yet it has received an immense amount of attention because of its remarkable role of at once identifying and distinguishing its bearer. The complete loss of hair makes most people feel intolerably conspicuous. As a current symbol of strength or beauty and as an essential physical characteristic, hair promises to continue to demand a major portion of dermatologic research efforts. Although the etiology of baldness is elusive much has been learned about hair and its growth.[13]

Chemically, hair is largely composed of the same protein, keratin, that gives the outer epidermal shell its outstanding stability. The hair cortex, however, is a "hard keratin" in contrast to the "soft keratin" characteristically found in the outer stratum of the skin. This keratin of hair has revealed much of its molecular mystery in the x-ray diffraction photograph. In the first place all mammalian hair, nails, hoofs, spines, horn and whalebone are basically of the same material — keratin. Secondly, hair may be best visualized or thought of as being composed of millions of long, submicroscopic fibers, all lying parallel to each other. With this in mind, it is easy to explain lengthwise hair splitting and the fact that in water hair swells more sideways than lengthwise. Actually, its diameter may increase by about 15 per cent, whereas its length may increase by only 1 per cent.

The keratin of hair is fundamentally the same as that of the epidermis, but in hair certain physical properties can be more dramatically demonstrated. The keratin molecule (alpha keratin) in normal unstretched hair is formed by regularly folded polypeptide chains, which can be pulled out straight to form a molecule twice as long (beta keratin).

As soon as the force is released, the hair returns to its former stable folded form, a remarkable example of elasticity. Water acts as the molecular lubricant for this smooth, gliding change. Thus, drying "sets" the hair temporarily. To improve upon the "permanence" of this keratin set, chemical

means have been used to break the cross linkages that would otherwise pull the molecule back into its contracted state.

The keratin of hair is elaborated by highly specialized epidermal cells at the base of the hair follicle. Hair growth is a complex histologic process that occurs in cycles. In man hair growth occurs at random so that there is a constant gentle shedding of hairs rather than any periodic mass effluvium. Actually, the cycle of any single hair varies from six months (body) to six or more years (scalp). Growth rate is variable, but in the month between barberings hair may increase as much as 1 cm. in length.

The rate of growth is greater in the presence of an elevated skin temperature, as in summer. Apparently, the mitotic rhythm is accelerated. In contrast illness may slow the growth gradient. However, nerves, diet, local massage and cutting are all essentially without effect on the growth of hair.

Hair growth in certain regions accurately reflects hormonal levels. The hair in the axilla and about the pubes reflects the ketosteroid activity of the adrenal cortex. Likewise, coarse hair on the chin and cheeks, as well as linear hair growth along the linea alba, have long heralded the rise in male-sex-hormone titer seen in adolescence.

Normal loss of hair from the scalp is largely the result of age and hereditary determinants. No direct hormonal correlations have been established, although the male type of alopecia is dependent on the presence of androgens.

Any alteration or interference with keratinization may lead to local or general alopecia. Epilation after radiation or radiomimetic drugs is an example of this. Another is the alopecia that follows severe infections.

The color of hair is due in part to melanin formed by the melanocyte. The quantity produced determines the degree of blackness. In the absence of melanin graying is seen. The color of red hair is not yet satisfactorily explained, but it has been shown that a special iron-containing pigment is probably partly responsible.

Sebum

Invisibly and continuously, another skin appendage, the sebaceous gland, manufactures an essential, oily lubricant. This product, called sebum, flows out from the hair follicle to form a surface film of microscopic breadth. Chemically, sebum contains fats, fatty acids, squalene and sterols.

The sebaceous gland is holocrine in nature since the cellular unit itself is shed. Here, the epidermal cells (which may be compared with the malpighian cells that form keratin and the melanocytes forming melanin) are exquisitely specialized for the production of a fatty emollient material. Each gland is usually found beside a hair follicle, as many as six glands sometimes discharging into the same follicle. On the head and trunk the sebaceous glands are most prominent and numerous. Distalward the extremities present fewer and fewer glands. Actually, the palms and soles are completely devoid of sebaceous glands.

Study of the physiology of these minute glands has posed distinct problems, many not yet solved.[14] It is not easy to observe activity of the gland directly, and indirect methods of collection have led to certain conflicting views. Only recently has the real significance of the surface flow of sebum been appreciated. Actually, Jones et al.[15] found that this skin fat could flow over moist skin with the astounding speed of more than 2.5 cm. per second; over dry skin, sebum flow was slow. All this has necessitated a re-evaluation of interpretation of sebaceous physiology with consideration of surface wetness. No studies have appeared that satisfy the new criteria posed by Jones and his associates. However, certain general observations seem well established on the basis of correlated findings. Sebum formation is critically elevated to a peak level during adolescence. Sebum production is greatest on the forehead, and in all areas the level of production varies directly with the numbers of glands to be seen histologically. Thus, the extremities show relatively little sebum formation. Prolonged exposure to a hot environment stimulates the gland. Furthermore, the glands are remarkably responsive to sex hormones. Androgens increase the number and size of sebaceous glands as well as their output. Estrogens have the converse effect. As in hair growth and keratinization, the nerve supply has no effect on sebaceous functions, nor can any change be effected by drugs or dietary maneuvers.

Apocrine Sweat

The apocrine sweat gland has been a subject of research in the dermatologic laboratory of the University of Pennsylvania for the past few years.[16] It is an interesting vestigial skin organ, found in man only in the axillary and anogenital regions. Actually a sexual characteristic, it first appears at puberty as a part of the pilosebaceous units that develop in these areas at this time. Just as there is no significant difference in axillary hair between the two sexes, there is no difference in the apocrine glands. Dependent upon the ketosteroid production of the adrenal cortex, they show some involution with age.

Interestingly enough, the mammary gland and also the ceruminous glands, producing ear wax, are variants of the apocrine sweat gland. From the evolutionary standpoint the apocrine gland may be considered to be a stage in transition between the sebaceous gland and the true highly specialized eccrine sweat gland. The gland derives its name

from its mode of secretion of part of the cell. Recent studies by Montagna et al.[17] indicate that the secretion may not be accompanied by the dramatic decapitation of the cell as commonly taught, but that the cells secrete via minute cellular extrusions. The decapitation seen in routine sections thus appears to be an artifact of fixation.

The apocrine gland typically buds from the hair follicle and forms a long excretory duct, which ends in a ball of coiled secretory tubules. This ball of tubules is barely distinguishable to the unaided eye as a yellowish mass in the lower portion of the dermis, close to the fat. Yet it has a volume a thousand times as large as the normal eccrine sweat gland.

Functionally, the apocrine gland forms apocrine sweat continuously. This is stored in the large tubules as in a reservoir, to be discharged to the skin surface at times of emotional stress or as a result of painful stimuli. Pharmacologically, epinephrine causes apocrine sweating. Completely unlike the eccrine sweat gland, the apocrine gland is unresponsive to heat or to acetylcholine.

To understand the mechanism of discharge of apocrine sweat requires a closer view of the histology of the gland. It is found that the entire apocrine tubule is invested with a thin syncytium of cells resembling smooth muscle. These cells, aptly named myoepithelium, provide a contractile force that sets up a peristaltic wave moving the sweat to the surface. This myoepithelium is a variant of smooth muscle and is supplied by adrenergic fibers of the autonomic nervous system. It responds to the local application of epinephrine or Pitocin but, strangely enough, not to histamine.

Apocrine sweat appears in small quantities as a turbid white fluid. Once the gland has been emptied — for instance after epinephrine — no further sweat can be made to appear for many hours.

Apocrine sweat is sterile, has a pH of about 6, and contains protein, carbohydrate and numerous inorganic materials. It is usually white, although yellowish hues may be present normally. The pigment responsible for the yellow color appears to be a lipofuscin. It is this pigment that gives apocrine sweat a definite fluorescence under ultraviolet light. Apocrine sweat may rarely show various colors, ranging from black to blue or green. My findings suggest that the same lipofuscins, but in a high state of oxidation, are responsible for this "chromidrosis."

Initially, apocrine sweat is odorless, but rapidly the skin flora and bacteria attack the organic material of the apocrine sweat. This results in the formation of pungent odors highly characteristic of the body odor associated with the axilla. Relative sterilization of the axillary vault by the use of such germicidal detergents as pHisoHex will completely inhibit odor formation.[18]

Eccrine Sweat

The eccrine sweat gland represents the "air-conditioning" unit of the body.[19] Here, in 2,000,000 units, spread over the entire skin surface, water is formed for evaporative cooling of the body. This gland is not a vital organ, for many born without sweat glands live in perfect health. Yet it is an organ that has permitted man to conquer continents previously completely uninhabitable. Man's physiologic economy is homeothermic, and environments can be tolerated only if constancy of internal temperature can be achieved in a very narrow band about the level of 98.6°F. The sweat gland serves this need well. It is efficient in supplying water to the surface in adequate amounts in response to thermal load and yet conserving electrolytes and organic material. Actually, but for osmotic limitations the eccrine gland would secrete distilled water.

The eccrine sweat gland is under neural control, being subserved by cholinergic fibers of the sympathetic nervous system. Thus, paradoxically, both sympathectomy and atropine result in absence of eccrine-gland response. The autonomic nervous control is mediated through the critical thermoregulatory centers of the hypothalamus.

Because of this elaborate neural control pattern, disturbances in sweating may be of considerable diagnostic assistance to the neurologist.

The gland consists of a small coil of secretory tubules and a long excretory duct passing through the dermis directly onto the epidermal surface. It is independent of the pilosebaceous apparatus. Actually, the sweat pore, like the follicular opening, is not a true aperture but a channel filled loosely with keratin that acts as a filter against ingress of foreign material.

Secretion from any unit gland appears in wave-like bursts. Here, there is no storage of sweat. It appears immediately and in the aggregate may constitute an enormous quantity. Volumes of over 3000 cc. an hour have been recorded. High sweating rates are maintained indefinitely in response to ordinary thermal demand. True fatigue of the gland cannot be demonstrated until after many hours of intensive stimulation. Reduction in sweat rate may also result from closure of the sweat pore and subsequent retention of sweat.

This leads the discussion to a consideration of experimental and clinical research on the sweat gland that has been the subject of intensive study for the past few years. This is the problem of sweat retention anhidrosis or a failure to sweat normally because of poral occlusion.[20] The pathogenesis of a wide variety of cutaneous disturbances has been elucidated by the demonstration that any minor nonspecific injury may interfere with the delicate process of keratinization, with subsequent closure of the sweat orifice by a keratotic cap or plug. These injuries include sunburn, maceration from sweat-

ing or under adhesive tape, irritation from antiperspirants such as aluminum chloride and damage from local heat or cold.

It is of interest to examine the sequence of events when sweating is stimulated after poral occlusion. In many persons no change can be noted except for the anhidrosis of the unit gland involved. In these the presence of the trapped sweat has apparently stopped further secretion. In others the sweat breaks through the duct and continues to be formed and to flow into the skin instead of onto the surface. This sweat may escape at various levels in the epidermis or dermis, and the clinical signs accurately reflect the level of rupture. In the absence of further injury the skin returns to its former normal keratinization cycle. In a few weeks the occluding keratin cap is shed, with subsequent restitution of the normal permeable keratinous sieve. Sweat is then delivered again to the surface, and the clinical signs promptly involute.

Summary

An attempt has been made to present modern trends in dermatologic research by a survey of current knowledge of six major specific functions of the epidermis: formation of keratin, melanin, sebum, hair, apocrine sweat and eccrine sweat.

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MEDICAL INTELLIGENCE

THE LOCATION OF LYMPHATIC INJURY BY THE USE OF SKY-BLUE DYE

Jack Gurwitz, M.D.*

HARTFORD, CONNECTICUT

In 1950 Weinberg and Greaney[1] first reported the identification of regional lymph nodes by the use of vital staining dye during operations for carcinoma. At that time they used pontamine sky blue in 2 per cent aqueous solution. Since then they have employed sky-blue dye,† 4 per cent solution, because of the rapidity with which the lymphatics and lymph nodes take up the dye.

In the case described below a lymphatic leakage followed ligation and stripping of varicose veins. As in many cases the varicose veins were quite troublesome, producing lymphatic fluid and leakage for a long time. It was easy to find the leakage with the use of sky-blue dye.[2, 3]

Case Report

G. R., a well developed and well nourished 44-year-old woman, was admitted to the hospital on July 2, 1953, because of bilateral varicose veins. A complete high ligation, with stripping, was accomplished. The convalescence was normal, and she was discharged on July 7. Three days later the sutures were removed from the wound, and a small collection of lymphatic fluid was noted in the left subinguinal wound. She was followed for 1 month and had to have aspiration of the lymphatic collection every 4 or 5 days because of the rapidity of the recurrence. On August 10 she was admitted to the emergency ward, where the wound was reopened under novocain anesthesia. The wound was searched, but no leakage could be found. The lower end of the skin flap was lifted, and 3 cc. of sky-blue dye was injected with a long needle into the deep fatty layers of the leg. Within a few minutes a spider-like network of blue dye was seen creeping up the subcutaneous tissue and entering into the surface of the wound. At one point a small drop of dye was visualized, leaving a vessel in the side of the wound. It was obvious that this was the injured lymphatic vessel. Silk sutures were then placed on each side of the leaking point, and the wound was closed in layers. The wound healed very well. There was no recurrence of lymphatic leakage. At one time the fluid was collected, and analysis showed a protein content of 2.8 mg. per 100 cc., which was consistent with lymphatic fluid in the extremities.

*Assistant surgeon, Mount Sinai Hospital.

†Processed by Wyeth, Incorporated, as a purified azo dye.

Discussion

Several similar cases have been observed in the past few years. Most of these patients have not been in too serious a condition but have been annoyed by the constant leakage of lymphatic fluid, which has required repeated aspiration and intervention. Because of the frequent intervention secondary infections have developed in a few cases. With this new technic it is simple to locate the leakage point and to eliminate it without great inconvenience to the patient.

This procedure should be kept in mind in a variety of surgical procedures. Frequently, thoracic and general surgeons have been concerned about cutting the lymphatic ducts and have had no way, at the time of operation, of identifying the point of leakage. With this technic many questionable injuries can be immediately checked before the surgeon closes the wound.

Summary

A case of lymphatic leakage in a subinguinal wound after high ligation and stripping of varicose veins is presented. A large collection of fluid developed within three or four days despite frequent aspirations and injection of sclerosing solutions.

The site of leakage was quickly and easily identified with the opening of the wound and the injection of a few cubic centimeters of sky-blue dye distal to the wound.

Less amounts of sky-blue dye can be used if hyaluronidase is mixed with the dye.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40061

Presentation of Case

First admission. A fifty-three-year-old dishwasher was admitted to the hospital because of exertional dyspnea.

The patient had been well until six years before admission, when he noted the gradual onset of exertional dyspnea and abdominal pain, relieved by rest. The pain was in the midabdomen and was described as a "gassy" sensation. It was unrelated to food, was brought on by constant exertion and was unrelieved by eructation or passage of flatus, but was quickly relieved by rest. He was hospitalized elsewhere and treated with digitalis and a low-salt diet, and advised to avoid exertion. He was told that an electrocardiogram showed only "extra beats." Apparently, he followed the regimen planned for him and subsequently experienced only an occasional recurrence of symptoms for several years. During the year before admission, however, the dyspnea had become worse; he slept on two pillows, and in recent months had paroxysmal nocturnal dyspnea about once a week. For the last seven or eight months he had episodes of aching abdominal and substernal pain that radiated to the left shoulder, lasting a few minutes, brought on by climbing a single flight of steps and occasionally occurring at rest. For two weeks he had had a mild unproductive cough.

He denied ever having had rheumatic fever, chorea, scarlet fever or syphilis. Cramps occasionally occurred in the right calf, without relation to exertion, usually about 4:00 a.m. He had drunk 10 to 15 glasses of beer a day for many years but had stopped drinking eight months before entry.

Physical examination revealed a hyperactive, florid man of medium build who was lying at a 10° angle in bed, coughing occasionally and not in pain. The neck veins were flat when he sat up, and the thyroid gland was questionably palpable. There was no bruit. The lung fields were clear except for diminished breath sounds at the right base posteriorly. The heart was enlarged, with the left border 14 cm. from the midsternal line and the apex at the sixth intercostal space. There was a high-pitched, harsh apical systolic murmur, but no diastolic murmurs. The aortic second sound was greater than the pulmonic. The rhythm was totally irregular, without deficit. The abdomen was normal; there was no peripheral edema. Arterial pulsations were palpable in all extremities. There was a slight fine tremor of the extended hands.

The temperature was 99°F., the pulse 104, and the respirations 20. The blood pressure was 154 systolic, 100 diastolic.

Urinalysis was negative. Examination of the blood disclosed a hemoglobin of 14.5 gm. per 100 cc., a white-cell count of 10,000, with a normal differential, and a prothrombin time of 16 seconds (normal, 14 seconds). The fasting blood sugar was 75 mg., the nonprotein nitrogen 31 mg., and the cholesterol 261 mg. per 100 cc. The bromsulfalein retention was 6 per cent. The blood Hinton test was negative. The basal metabolic rate was + 11 per cent, and the radioactive iodine uptake 43 per cent. An electrocardiogram demonstrated atrial fibrillation and left-bundle-branch block. A roentgenogram of the chest showed a cardiothoracic ratio of 18.5:31.5, with enlargement of the left ventricle. The aorta was tortuous. Thickening of the right pleura was noted, and encysted fluid was observed in the lesser fissure (Fig. 1 and 2).

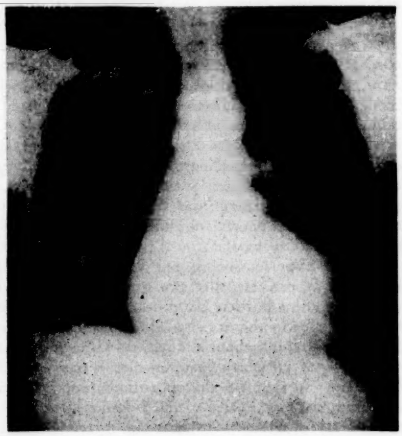

FIGURE 1. *Anteroposterior Roentgenogram of the Chest. Note the marked cardiac enlargement and the fluid within the minor septum caused by congestive heart failure (indicated by the arrows).*

The patient improved on a program of salt restriction, mild sedation, digitalization and erythrol tetranitrate, 15 mg. four times a day, until the seventh hospital day, when severe, steady mid-abdominal pain without radiation suddenly occurred. He was pale, sweating and nauseated and vomited once. The blood pressure was 168 systolic, 100 diastolic, and the pulse 92. An electrocardiogram revealed no changes from the earlier tracing. There was no abdominal tenderness or spasm, and peristalsis was normal; a finger specimen of stool was ++ guaiac positive, and the white-cell count was 19,000. A plain film of the abdomen demonstrated no distention of the bowel, free air or opaque calculi. During the next twenty-four hours the temperature rose to 100°F., and the white-cell count to 23,000; the pain persisted. Several guaiac-positive stools were passed, and the patient continued to vomit clear material. Moderate right-lower-quadrant pain, tenderness and muscle spasm developed. Abdominal exploration was performed, an embolus to a branch of the ileocolic artery was identified, and 126 cm. of terminal ileum, with 12 cm. of colon, was removed. About twelve hours later the left leg appeared purplish and cool, and the left femoral pulse was weak. A short time later an embolus was removed from the left common iliac artery.

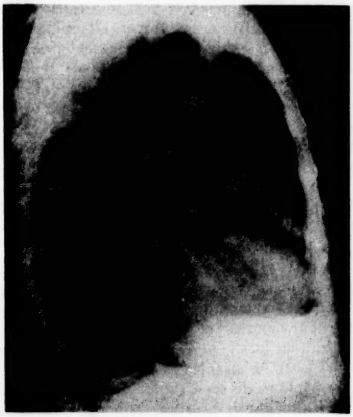

FIGURE 2. *Lateral View.*

Convalescence was satisfactory, and he was discharged to a nursing home on the eleventh postoperative day. He was taking digitalis, 0.1 gm. a day, and erythrol tetranitrate, 15 mg. four times a day.

Final admission (four months later). During the interval since discharge he had done well, returning to work after four weeks of limited activity. He had a few episodes of exertional pain relieved by nitroglycerin and was troubled by frequent soft stools. Twelve days before the final admission the chief complaint was painful hemorrhoids. He was taken to the Emergency Ward after being found unresponsive in his room.

On admission he was stuporous but moved all extremities. There was marked cyanosis and irregular breathing. There was no odor of alcohol or acetone to the breath. The lungs were clear. The heart had a diastolic gallop and a rate of 180. There was a Grade 2 systolic murmur at the apex. The liver edge was palpated three fingerbreadths below the right costal margin and felt slightly irregular. Reflexes

were equal bilaterally with extensor plantar and absent abdominal reflexes.

The temperature was 98°F., the pulse 180, and the respirations 24. The blood pressure was 94 systolic, 80 diastolic.

The urine was again normal, with a specific gravity of 1.025. Examination of the blood revealed a hemoglobin of 14.5 gm. per 100 cc., a white-cell count of 6500, a sugar of 115 mg. and a nonprotein nitrogen of 23 mg. per 100 cc., and a carbon dioxide of 25.5 milliequiv., a sodium of 140 milliequiv., a potassium of 6.0 milliequiv. and a chloride of 107 milliequiv. per liter. Lumbar puncture showed an initial spinal-fluid pressure equivalent to 175 mm. of water, with normal dynamics. The tap was traumatic, and the fluid contained 40,000 red cells and 250 white cells per cubic millimeter. The supernatant fluid was clear; the total protein was 56 mg. per 100 cc., and the globulin ++.

The patient remained stuporous and died four and a half hours after admission.

Differential Diagnosis

Dr. Conger Williams*: This fifty-three-year-old man had symptoms for six years, with proved emboli four months before death, and finally died in coma without localizing signs. It remains to be seen whether I can tie all this together with one diagnosis. It is possible to do so, I think, with some qualifications. I thought it possible, although not certain, that the congestive heart failure had actually extended over a period of six years since the symptoms that he first complained of were exertional dyspnea and pain in the abdomen that was definitely related to effort. He had another discomfort described later, that seemed to be related to effort. Many patients with congestive heart failure in association with mitral stenosis and other lesions that produce a considerable degree of right-sided failure complain of pain with effort. The pain probably results from hepatic engorgement and is usually located in the right upper quadrant or in the epigastrium. It is impossible to say from the data given in the protocol whether he had coronary insufficiency or mitral stenosis, but I suspect that he had congestive heart failure at the time the symptoms began. The fact that he was treated with digitalis very early in the illness and that the dyspnea on effort was progressive over the course of several years also suggests that the trouble began with congestive heart failure.

To go on to the first hospital admission, What were the significant findings at that time that might lead one to a definite diagnosis of heart disease? In the first place the neck veins were mentioned as being flat. Unless a definite statement is made about absence of pulsation in the neck veins, elevated venous pressure cannot be ruled out. Secondly, he had cardiac enlargement on physical and x-ray examination. Also, the electrocardiogram showed atrial fibrillation, and I suspect that this arrhythmia had been present for a long time. Nothing in the history tells me exactly when the fibrillation began, but this may have been the reason why digitalis was started at the onset of the illness. Since it can be established with reasonable certainty that he had heart disease, the next question is, What was the etiology? I thought it was difficult to explain the course and the findings entirely on the basis of valvular disease from the evidence given here — he had only a Grade 2 systolic murmur. We have seen a few patients with mitral stenosis who have had no audible murmur. However, this is a rare situation.

Another important finding on the first hospital admission was that of left-bundle-branch block, which does not necessarily tell us much, since it is present in association with many diseases. Of course, coronary-artery disease is statistically the most common etiologic factor associated with bundle-branch block. However, bundle-branch block is of importance by itself in that it frequently obscures significant diagnostic patterns. I should like to know whether the electrocardiogram showed the pattern of hypertrophy of the left or right ventricle or whether he had myocardial infarction in the past. All these possibilities become obscured when left-bundle-branch block develops.

He had hypertension of not very great degree; I thought it possible that the hypertension added somewhat to his burden, but I doubt if hypertensive heart disease was the principal mechanical fault. Another thing to think about in a patient with symptoms suggestive of coronary insufficiency is myocardial infarction. Again, the electrocardiographic pattern obscured any such evidence, and I do not know from the history whether a myocardial infarction ever occurred. It might have explained at least one of the episodes of embolism, but since I cannot point definitely to a history suggesting infarction, I shall have to discard that.

Cor pulmonale, which in turn gives rise to hypertrophy of the right ventricle, is another of the diagnoses that might well have been obscured by the electrocardiographic abnormality. Patients with chronic cor pulmonale occasionally turn out to have had multiple pulmonary emboli over a long period. Again, I am forced to abandon that diagnosis for lack of more specific evidence. This might be a good time to see the x-ray films.

Dr. Stanley M. Wyman: The original examination of the chest shows the much enlarged heart; I do not know whether the enlargement is entirely of the left ventricle — there may be some hypertrophy of the right ventricle as well. The encapsulated fluid is localized in the minor interlobar fissure (Fig. 1). In the lateral view (Fig. 2) the characteristic tapering, slender ends are apparent. There is little to suggest pleural fluid elsewhere in

*Associate physician, Massachusetts General Hospital.

the chest. The hilar vessels are not particularly engorged; the lung fields are quite clear. In the film taken two days later the density has cleared completely, demonstrating the main differential point between fluid and a solid tumor. The film of the abdomen taken during the acute episode shows no dilatation of either large or small bowel, no abnormal visceral shadows and no stones. The last pair of films demonstrates recurrence of the fluid in the minor fissure and at this time there is a small amount of fluid elsewhere in the right pleural space.

DR. WILLIAMS: That is a nonspecific picture of cardiac enlargement, perhaps subsiding failure, suggested by the fluid. Do you agree that the fluid in the interlobar space is consistent with subsiding congestion?

DR. WYMAN: Yes.

DR. WILLIAMS: To explain the emboli, I have already mentioned one possibility, infarction, only to discard it. The presence of atrial fibrillation is of possible importance in connection with these emboli.

Another condition causing a nonspecific cardiac enlargement of this sort that I might consider is a diffuse process involving the myocardium alone. Several years ago, when it was the fashion to group together all sorts of diffuse myocardial diseases under the name of Fiedler's myocarditis, the frequent occurrence of emboli in such cases was stressed. Mural thrombi on the endocardial surface of the ventricles was the source of such emboli. An infectious endocarditis is unlikely because of the history, which went back at least six years. This man was a heavy drinker, but again the long history is against beriberi as a possible etiology.

Another diagnosis that is being made more and more and many of us have missed in the past is subendocardial fibrosis or subendocardial fibroelastosis. That descriptive term is given to a disease process of unknown etiology that primarily involves the endocardial surface but also sometimes involves the myocardium. It is frequently associated with emboli. I saw a case recently* in which the diagnosis of coronary-artery disease had been considered for many years because the patient had what seemed to be classic symptoms of coronary insufficiency. I think that of all the diagnoses this most satisfactorily covers all the findings.

One other thing I should like to mention before concluding is that I am not sure of the nature of the final episode, characterized by coma. It seems unlikely that this was embolic in the usual sense because of the lack of localizing symptoms. This patient went into coma and died without any specific neurologic pattern besides the coma. Was this metabolic death? Had he been on the edge of hepatic failure and perhaps been pushed into hepatic coma? Obviously, the course was much too short for that. I do not know if he ever received ammonium chloride, which is known to be the precipitating factor at times in patients who have both liver disease and heart disease and are receiving the drug for therapeutic reasons. He may have had a subarachnoid hemorrhage that was covered up by the trauma of the lumbar puncture.

In summarizing this case I believe that the patient probably had endocardial fibroelastosis with cardiac enlargement and repeated emboli. The final episode of coma was unexplained, but I doubt if it was due to emboli.

*Case Records of the Massachusetts General Hospital (Case 39441). *New Eng. J. Med.* 249: 734-738, 1953.

CLINICAL DIAGNOSES

Coronary-artery disease.
?Pulmonary emboli.
?Cerebral emboli.
?Toxic encephalopathy.

DR. CONGER WILLIAMS'S DIAGNOSIS

Cardiac hypertrophy with subendocardial fibroelastosis and emboli.

ANATOMICAL DIAGNOSES

Idiopathic cardiac hypertrophy, with endocardial fibroelastosis.
Congestive heart failure, with pulmonary congestion and edema, hepatic congestion and ascites.
Renal infarct, old.

PATHOLOGICAL DISCUSSION

DR. ROBERT H. FENNELL, JR.: The principal finding at autopsy in this patient was definite evidence of congestive heart failure, with pulmonary edema and congestion; the liver was severely congested, and there was some ascites. The heart was quite large, weighing 530 gm. All the chambers were dilated. The left ventricle was rather thick, measuring 17 mm., and the right was also thick, measuring 5 mm. The endocardium was thickened diffusely to a mild degree. This was most marked near the outflow tract of both ventricles and was not present to the degree that we have seen it in some of these cases of endocardial fibroelastosis. The valves were perfectly normal, with no evidence of damage. The myocardium was normal in appearance and consistence except for a small area of scarring in the apex. Microscopically, there was little damage in the myocardium, only very slight scarring being present. The endocardium was thickened but not to the degree that we have seen in other cases, although I think that there was enough to allow me to call this endocardial fibroelastosis. Where the emboli were forming, I am not sure. There was thickening of the endocardium in the left atrial appendage and a bridging between the interstices such as one sees with organized thrombi. There was no evidence of thrombi in the left ventricle.

The impressive thing about this case was the coronary arteries, which were completely normal. They were as smooth, soft and pliable as those in young people. The brain showed nothing but one small, old infarct, so that I suppose that the terminal changes must have been on a metabolic basis as part of the congestive heart failure. Although there was no evidence of emboli in the brain, there was evidence of emboli in the kidneys, with many old infarcts. This, then, appears to have been a case of idiopathic cardiac hypertrophy, with some degree of endocardial fibroelastosis.

DR. WILLIAMS: Do you suppose hypertension was a factor?

DR. FENNELL: Hypertension was present to a mild degree; the blood-pressure readings in the last months ranged from 140 to 150 systolic, 90 to 100 diastolic. Whether or not hypertension was present several years before admission I cannot say, but the hypertension that we know about does not explain the hypertrophy. The amazing feature of this case, however, is the angina in the presence of normal coronary arteries. Not even a little sclerosis was present. Patients with greatly thickened left-ventricle walls sometimes have angina, but the ventricle here measured only 17 mm. which is not impressive. Endocardial thickening has been given as an explanation for angina, but the case Dr. Williams referred to, and this one, are the only ones of this type with clear-cut angina pectoris. I cannot explain the angina.

CASE 40062

PRESENTATION OF CASE

A forty-six-year-old widow (gravida 2, para 2) entered the hospital because of abdominal pain.

The patient had been in good health until the day before admission, when she began to have sharp, severe crampy pain in the lower middle portion of the abdomen that radiated into both lower quadrants, the left hip, the lower back and the rectum. The pain was constant and became increasingly severe. She was nauseated and had a temperature of 101°F. on the morning of admission, but there were no chills, vomiting, diarrhea, constipation or urinary difficulty. She had had several similar episodes in the past; the last one, which occurred five months previously, was associated with chills, fever and crampy pain in the lower abdomen going down to the anterior thighs. For the past week she also had a "cold" with a slight sore throat. The menstrual cycle had been regular at twenty-eight-day intervals, the flow lasting about three days. The last period occurred about eight days before entry and lasted for two days, with less flow than usual. She had sexual intercourse regularly without using contraceptives up to a month before admission. She had had a yellow vaginal discharge, which she treated with douches two or three times a week. There had been no recent increase of the discharge. She denied previous venereal disease.

Physical examination revealed an inflamed throat, clear chest and normal heart. There was tenderness in the left lower quadrant, but no spasm, mass or rebound tenderness. Peristalsis was normal. On pelvic examination the external genitalia were normal. The cervix was slightly tender when moved, and there was a small amount of bloody mucus at the external os. The uterus was movable, normal in size and nontender. The right vault was clear; in the left vault there was a tender, 4.5-cm., movable mass. A 3-cm., tender, fixed mass was palpable in the right side of the cul-de-sac.

The temperature was 100°F., the pulse 90, and the respirations 22. The blood pressure was 120 systolic, 64 diastolic.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 12.5 gm. per 100 cc. and a white-cell count of 15,200, with 92 per cent neutrophils. The culture of the cervical material grew out a few diphtheroids. A pregnancy test was negative, as was cytologic study of the vaginal smear.

In the hospital the patient ran a low-grade fever, with elevations of temperature to 101°F.; however, after five days of penicillin and streptomycin therapy, the temperature reverted to normal and she had very little discomfort. Although she remained afebrile, on the ninth day she again complained of pain in the back, left groin and upper thigh. Two days later an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD HAMLIN, JR.*: As I read this protocol it seemed to me that there was little information aside from the fact that a middle-aged woman presumably had a low-grade pelvic peritonitis associated with masses. Given that information, there

*Associate visiting surgeon, Massachusetts General Hospital.

seems to be practically no limit to one's speculation. Perhaps the inexplicable eleven-day hospital stay before the operation may be pertinent, but I am unable to think of a good reason why that should enter into the diagnosis. In dealing with a low-grade peritonitis, one must think of bacteria that do not cause massive overwhelming sepsis or of blood — anything that irritates the peritoneum may produce a course similar to that which the patient had.

The first consideration is the possibility of blood in the pelvis. Obviously, the information given suggests an ectopic pregnancy. There had been obvious exposure, and the last period had been somewhat abnormal in that it was shorter, with less flow. The pain was compatible with that of an ectopic pregnancy. Loose blood in the peritoneum would produce the constant irritation, but it would be unlikely to cause the temperature to rise to 101°F., although that is not impossible. The white-cell count and differential count are consistent with hemorrhage although there was no evidence whatsoever of loss of any large amount of blood. If the patient was allowed to remain in the hospital for eleven days with an ectopic pregnancy, that was most unfortunate. Although I cannot rule out an ectopic pregnancy, I am not inclined to believe that was the diagnosis.

As I talked about ectopic pregnancy, the possibility occurred to me that I am being put on the same spot as the resident in the emergency ward was and that the history was a fabrication. It is possible that this woman had an abortion and did not let the resident know. The story and findings are perfectly consistent with an abortion. An abortion would explain the bloody mucus in the external os, the peritoneal pain and the pelvic cellulitis. I am unable to rule that out, and I mention it because I believe that thought should occur to everyone who sees a patient under similar circumstances or else he may misjudge the situation.

The rupture of an endometrial cyst could have produced this picture. She may well have had endometriosis. Nothing was said about whether she had dysmenorrhea in the past, but considerable endometriosis may be present without dysmenorrhea.

The twisting of a simple ovarian cyst or dermoid cyst or something of that nature seems to be far less compatible with the history. The onset of pain with a twisted cyst is usually extremely abrupt; the pain may vary in intensity, and it persists as long as the lesion is allowed to remain. Almost invariably, at least in my experience, it is associated with vomiting. This patient was carefully described as having no gastrointestinal symptoms. Although the lack of vomiting does not rule out twisted cyst it makes that diagnosis seem far less likely. Nor do the adjectives that were used convey to me the idea of a twisted ovarian cyst.

It is difficult to eliminate even such entities as appendicitis and diverticulitis, both of which are possible under these circumstances. The careful ruling out of other symptomatology makes it extremely unlikely, and I shall simply mention them to put them aside.

Another entity that one must consider is pelvic inflammatory disease. When I was a house officer in the emergency ward pelvic inflammatory disease was one of the most common causes of admission: the wards were full of patients who were being treated in various ways. I have not seen a case that I recognized as such for a long time. The findings and history are consistent with pelvic inflammatory disease that was recurrent. Of course, the recurrence, which I have not mentioned before (she had several similar episodes in the past), makes such conditions as an abortion less likely. It does not rule out any of the other entities that I have mentioned, but it also makes them less likely. Pelvic inflammatory disease is usually recurrent. Everything in the protocol is completely consistent with it.

The impression I get from reading the description of the physical examination is that the pelvis was not particularly painful. Perhaps I am inferring something that was not given, but I have the impression that the uterus and the mass in the left vault could be moved and that they were tender, although not excruciatingly so, as one would expect with most of the entities that I have mentioned. Pelvic inflammatory disease usually causes extreme tenderness. That the mass in the left vault was described as being movable is also consistent. Such a mass with pelvic inflammatory disease may be movable although the masses are usually fixed as the mass in the right adnexa was described as being. The white-cell count was slightly higher than I recall with pelvic inflammatory disease but is not inconsistent. The lack of a positive culture from the cervix is not disturbing because, unless a careful attempt at culturing on suitable mediums is made, it is negative. Nothing was said about a cervical

smear, which used to be done routinely in the emergency ward. Because pelvic inflammatory disease is by far the most common cause of pelvic pain, because the disease subsided on antibiotic treatment and because it is completely consistent with the data given in the protocol, I am going to make that diagnosis.

DR. JOSEPH C. AUB: I am impressed by the accuracy of the surgeons in arriving at the size of the mass as 4.5 cm. It must have been a very hard mass to be as circumscribed as that.

DR. HAMLIN: That was what I was implying when I mentioned the lack of tenderness; usually, when a mass is tender, one cannot determine its exact size.

DR. AUB: It makes me recall a clinicopathological conference in India at which Dr. Pietro Valdoni, of Rome, made the diagnosis of a retained head after an abortion and that was correct.

DR. LEWIS W. KANE: Would you consider that the infecting agent was the tubercle bacillus?

DR. HAMLIN: I have seen only a few cases of tuberculous pelvic peritonitis — perhaps 2 or 3. None of the patients had much pain or temperatures as high as this. I cannot rule it out, however.

DR. HOWARD ULFELDER: I believe that Dr. Hamlin has covered the ground very well indeed. He was quite right in emphasizing that the previous attacks of similar discomfort were also inflammatory. The patient had not only pain but also fever and chills, which to me means that she had an inflammatory lesion from the start. The organism involved, therefore, was one that the body was able to handle quite well by itself such as the gonococcus. I think this was a new episode of acute inflammation superimposed on a prior chronic inflammatory disease of the tube and ovary.

DR. BENJAMIN CASTLEMAN: On the ward when she first came in the physicians thought seriously of an ectopic pregnancy, but when the pregnancy test was reported as negative and the findings were further evaluated, they came to the same conclusion as Dr. Hamlin did.

DR. HAMLIN: I meant to say something about that. The fact that the Aschheim–Zondek test is negative in no way rules out an ectopic pregnancy. It has been demonstrated, I cannot remember by whom, that the Aschheim–Zondek test is positive in only about 50 per cent of cases of ectopic pregnancy.

CLINICAL DIAGNOSIS

Pelvic inflammatory disease.

DR. EDWARD HAMLIN, JR.'S DIAGNOSIS

Pelvic inflammatory disease.

ANATOMICAL DIAGNOSIS

Acute and chronic salpingoöphoritis, left.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation, a large distended tube was found on the left side. The proximal end of the tube was narrowed but thickened, and its surface was very hemorrhagic and covered with fibrin. Beyond the narrow point the tube suddenly expanded into a retort-shaped, thick-walled inflammatory salpingitis. The ovary was adherent to the tube. The point of narrowing was not a twist but a stricture; there was no evidence of infarction of the tube or ovary. In the distended tube we found a fair amount of pus so that, as Dr. Hamlin said, this was an example of the type of pelvic inflammatory disease that we do not see very often at present.

DR. HAMLIN: One of the diagnostic aids in pelvic inflammatory disease that we used to think about was tenderness in the right upper quadrant caused by a perihepatitis; it seemed to occur in about 50 per cent of the cases of salpingitis.

DR. CASTLEMAN: Ordinarily, both tubes are involved. In this case the surgeon believed that the right tube and ovary were normal and did not remove them or the uterus.

DR. KANE: What did the microscopical sections show?

DR. CASTLEMAN: They showed an acute and chronic inflammatory reaction destroying the wall of the tube with polymorphonuclear cells, lymphocytes and plasma cells. No tubercles were observed.

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PRESENT STATUS OF RESEARCH ON VACCINATION AGAINST POLIOMYELITIS

RESEARCH on vaccination against poliomyelitis has entered its most promising phase during the past two years as a result of the discoveries of Enders, Weller, and Robbins,[1,2] which demonstrated that all 3 types of poliomyelitis virus can be propagated in cultures of non-nervous tissue and that the presence or absence of virus can be established by cytopathogenic effects in vitro. There are two main approaches to the problem: preparation of a killed-virus vaccine that is antigenic in small enough dosage to permit its manufacture for many millions of persons, and at the same time sufficiently stable and devoid of dangerous side-effects to make it practical; and discovery or development of avirulent (nonparalyzing) variants of the three immunologic types of virus that might prove as effective against poliomyelitis as the 17-D variant is against yellow fever or vaccinia against smallpox. The final answer to the question whether any vaccine is really effective in preventing the natural disease can come only from carefully controlled experiments on tens or hundreds of thousands of children, and public-health officers and physicians all over the country have recently been asked to co-operate in such an experiment by the National Foundation for Infantile Paralysis. Since human experiments on so large a scale do not lend themselves to frequent repetition, it is highly desirable to seek a dispassionate analysis of the scientific data on which such an experiment must be based as well as to consider the consequences of a successful or unsuccessful outcome.

Although no new scientific discoveries are required to determine whether or not a suitable killed-virus vaccine can be developed for a specific human experiment, a tremendous amount of work by quantitative standardized assay methods must be carried out before one can be certain that results obtained in small exploratory tests are sufficiently reproducible to warrant the performance of the larger tests. Excellent work along these lines has been performed by Salk and his associates, but publications of systematic work on this phase of the problem from any other laboratory are not available. From Salk's[3] first preliminary report it appeared that 0.3 to 1 cc. of formalinized tissue-culture fluid, administered with adjuvants in one or more doses, effectively boosted the level of antibody in children who already possessed some as a result of previous infection with one or more types of poliomyelitis virus, but no evidence was presented that this amount of vaccine with adjuvant could produce antibodies for the important Type 1 virus (the type responsible for almost all epidemics) in children who had no antibody to begin with. In the second preliminary report[4] evidence is presented that 9 children without antibody for any of the 3 types of virus developed antibody for all 3 types in titers of 1:4 or more after 3 intramuscular injections of 1 cc. of aqueous vaccine without adjuvant at weekly intervals. In another test with 0.3 cc. of aqueous vaccine given intracutaneously three times at

weekly intervals, 2 of the 6 children tested failed to show antibody for the Type 2 virus, whereas all developed antibody for Types 1 and 3. Whether or not the small amounts of antibody developing after aqueous vaccine are as effective against other strains as for those used in the vaccines is not known, nor is it known whether the antibody persists for as long as six to eight months. These findings are nevertheless most encouraging, particularly if it can be shown that they can be regularly obtained with vaccines having a certain minimum standard of antigenic potency as determined by a reproducible method of assay. No data have as yet been presented on any method of assay or on stability of stored vaccines. The preliminary tests on children were all made with vaccines inactivated by a 1:250 dilution of formalin at 1°C., whereas the vaccines that are to be used in the projected human experiment are to be inactivated by a 1:4000 dilution of formalin at 35°C.; no data have been offered to show that they will still be of adequate potency several months after preparation at the time they will have to be used. Concern has also been expressed[5] about the use of the virulent Mahoney strain of virus in the vaccine, minimal amounts of which cause paralysis more readily by the intramuscular than by the intracerebral route, and a safety test even on 50 monkeys does not eliminate the possibility that 1 in 1000 or 1 in 10000 would be paralyzed. Other Type 1 strains of virus that do not possess this property could undoubtedly be substituted in vaccines that are to be used in hundreds of thousands of human subjects.

The projected vaccines are to be made from the kidneys of rhesus monkeys, which of necessity retain a certain number of red cells, and one would want to make certain that repeated injections would not sensitize Rh-negative girls enough to cause a greater than ordinary chance of damage to later Rh-positive offspring. The results of such tests, as well as of tests for potential nephrotoxic effects, should be presented before a mass trial is begun. No one can fail to agree with Salk's[4] statement: "We do not want to allow any distortion of the fact that we are still actively in the stage of clinical investigation; and that this work must be continued, but it must be continued gradually and cautiously." It also seems that systematic work on so important a problem should be pursued in more than one laboratory, and it is surprising that the fine teamwork that the Foundation successfully used to help obtain a conclusive enumeration of the types of poliomyelitis virus[6] has not been utilized in this most important project.

The potential development of a vaccine incorporating living, avirulent strains of poliomyelitis virus has been advanced by Sabin's recent discovery that all 3 immunologic types of poliomyelitis virus could be converted from virulent to avirulent forms by special methods of cultivation in non-nervous tissue. The data he presented at the December, 1953, meeting of the New England Pediatric Society indicated that the work had progressed sufficiently to warrant the extensive laboratory studies that must precede any tests on human beings. The prospect of an effective and practicable method of vaccination against poliomyelitis seems better now than ever before, but there may be considerable wisdom in making haste slowly.

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PIERIAN SPRING

THE chairman of the Committee on Postgraduate Medical Education of the Massachusetts Medical Society, in his "Reflection on Postgraduate Education," published as a special article in this issue of the *Journal*, is quite naturally presenting a brief for the Postgraduate Medical Institute, of which he is president. For the Institute is at least the ward of his committee if not, indeed, its begotten child — like John Henry, already grown larger than the parent.

Dr. Ellis stresses the importance of continuing professional education for the practicing physician,

on the assumption that the rural practitioner needs it most of all — not because of any special defects in his earlier education but because of his relative isolation from the stream of medical progress. This concern for the country doctor, however, should not lead to a lack of consideration of the general practitioner in the purlieus of the cities and in their underprivileged sections, where some of the worst possible medicine is sometimes practiced, as Collings and Clark* have indicated.

Despite sporadic and isolated efforts that have long been made in the direction of physician education, the problem, according to Ellis, has been almost universally neglected by both the medical schools and the foundations, which should be the natural candidates for the role of rescuer. More recent stirrings on the part of the practicing profession itself have been shown in the establishment of the Section on General Practice of the American Medical Association and the founding of the Academy of General Practice, perhaps the first such organization to require its members to drink regularly at the fountainheads of medical knowledge.

What postgraduate medical education needs most, however, is an intelligently organized and concentrated effort to carry inspired and inspiring teaching into the field, in some form other than that of didactic lectures delivered by ill prepared instructors to unresponsive audiences. It is almost trite to say that effective physician education is synonymous with the activities of a modern hospital in which interns, residents and undergraduate medical students are also eagerly learning the philosophies and the technics of the world's most absorbing profession.

Ellis's experience with the Postgraduate Institute that has risen under the aegis of his committee has convinced him that "an approximation of the medical teaching center" can and must be developed in the community hospital. To function properly as foci of teaching as well as of service, these hospitals, each of which cannot help being radially located in relation to some centers of medical progress, must be closely bound to its inspirational source. From the central schools and hospitals consulting and teaching personnel can be piped to the peripherally located institutions, the regulation of such flow being quite properly a function of a postgraduate institute.

Simply to expose a busy and often weary practitioner to an opportunity for betterment may not always be enough, however. Some, but not all of them, will have the desire and the peculiar power of levitation needed to raise themselves by their own bootstraps. Thought must also be given to the organization of the practitioner's life and practice so that he will be able to utilize the efforts being made so earnestly in his behalf.

*Collings, J. S., and Clark, D. M. General practice today and tomorrow. *New Eng. J. Med.* 248:141-148, 1953.

PHYSICIANS' SICKNESS INSURANCE

In a discussion of the problems of sickness insurance recently reported in the *British Medical Journal*,† Mr. E. A. J. Heath, manager of the Medical Sickness, Annuity and Life Assurance Society, presented some interesting figures on the types of illness experienced by physicians themselves.

A comparison of the years 1937 and 1952 showed an actual reduction in the rate of claims, which was obviously due to the occurrence of an influenza epidemic in the former year. Aside from this special factor it was interesting to note that no general increase in claims had occurred, as had been experienced in industry.

Specifically, claims for septic infections had been three times commoner in 1937 than in 1952, claims for appendicitis had been halved in the latter year, for no apparent reason, and those for scarlet fever and diphtheria had disappeared. Pneumonia had occurred more frequently, although it entailed a shorter period of disability, and was practically nonfatal.

The claims that had increased, to balance the ledger, were those for virus infections, for disk injuries, possibly for cancer and predominantly for coronary thrombosis. The 35 disk injuries in 1952 represented a shift from the claims paid in 1937 for lumbago, sciatica and sacroiliac strain, which were on the average of short duration; considerably longer periods of disability were claimed for the disk injuries, but with increasingly conservative treatment coming into vogue.

†Doctor's diseases. *Brit. M. J.* 2:1372, 1953.

Coronary thrombosis has become "the biggest medical problem which life office actuaries have to face today, and it is even more important in the sickness field." The present expectation is that 20 per cent of those joining the society at the usual age will suffer from coronary-artery disease before reaching the age of sixty-five and a third of all the deaths will result from this particular expression of the aging process.

CALIFORNIA TELLS THE WORLD

THE California Medical Association has launched its own undergraduate and postgraduate program for medical education, but on a far different order than that of the Postgraduate Medical Institute sponsored by the Massachusetts Medical Society and currently flourishing at 22 The Fenway, Boston. East is East and West is West, and their meeting grounds are various.

California's newest venture into the field of medical education, as approved by the Association's House of Delegates in December, consists of the Audio-Digest Foundation, a nonprofit corporation subsidiary to the Association. As its name suggests, its function will be the summarizing and recording on tape and synchronized visual slides or film strips of current medical literature and lectures. This material, which will be selected and prepared by a board of editors representing all the specialty groups, will be distributed to physicians wherever they may be found in circumstances that will permit their subscribing to it. The service will be beamed along three slightly divergent channels — to the specialist, to the general practitioner and to the medical student.

A weekly one-hour tape recording already summarizes the current medical literature from approximately 600 journals for the benefit primarily of the general practitioner; this service has been operating on an experimental basis since last March and has proved so successful that subscriptions are currently in operation throughout the accessible regions of the globe. On January 15 a biweekly service became available for surgeons, and on February 15 one for internists will swing into action. All lecture material, according to a news release from the Association, will be reviewed twice yearly.

Along the same lines a complete medical lecture library is being established with material "accumulated from on-the-spot recordings at medical conventions," and lecture tapes preserving the ruminations of the leading professors in the nation's 79 medical schools are in process of being assembled. These tapes will encompass the entire field of undergraduate education.

California thus maintains its reputation for doing things in a big way — high, wide and handsome. That the jaded East may not seem too hopelessly outdistanced, however, a distinguished medical journal published in New York and edited in Boston has within a few weeks staked its own claim to a world market for scientific communication. For *Blood — The Journal of Hematology* has, in the words of its publishers, opened a major breakthrough in the great barrier of language. This consists of published summaries of its articles in "Interlingua," the new supranational language — a language not constructed, in the sense that Esperanto and others have been artificially developed, but one extracted and synthesized from all the elements common to the various languages of Europe.

Thus does the Battle of Communication continue to be waged.

PRIZE ESSAY COMPETITION

The $100 prize-essay competition for fourth-year students closes March 15, 1954.

Full details were published in the *Journal* of October 22.

Physicians are better qualified for general travellers and explorers than any other class of educated men, as they are held in universal estimation by barbarians and savages.

Boston M. & S. J. *February 15, 1854*

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

This year the Committee on Finance has voted a refund of $4000 to the district societies from the surplus in the General Fund at the end of 1953.

Members are reminded that the percentage of this sum that is allocated to their own district is determined by the number of dues from that district paid by March 1, 1954. Members who have not paid their dues by this date are automatically removed from the mailing list of the *Journal* until such dues are paid.

ELIOT HUBBARD, JR.
Treasurer

DEATHS

QUINCY — Josiah E. Quincy, M.D., of Boston, died on January 27. He was in his fifty-eighth year.

Dr. Quincy received his degree from Northwestern University Medical School in 1922. He was a member of the staffs of the Massachusetts Eye and Ear Infirmary and the Faulkner Hospital, as well as a member of the New England Oto-Laryngological Society, and a fellow of the American Academy of Ophthalmology and Oto-Laryngology.

He is survived by his widow, three daughters, a brother and a sister.

SCIGLIANO — Frank P. Scigliano, M.D., of Belmont, died on January 26. He was in his fifty-fourth year.

Dr. Scigliano received his degree from Tufts College Medical School in 1926. He was a member of the staffs of the Cambridge City and Somerville City hospitals, and was formerly president of the Italian Medical Society of Boston.

He is survived by his widow, a son and a daughter.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

RETIREMENT OF DR. HINTON

After thirty-eight and a half years of service as director of the Wassermann Laboratory of the Massachusetts Department of Public Health, Dr. William A. Hinton retired on December 31. Since he assumed charge of the laboratory when it was organized in 1915 the volume of tests has risen from 100 to 2000 per day. The serologic test for syphilis that bears his name is used in many laboratories outside Massachusetts. The Davies-Hinton test has proved its reliability in the detection of syphilis of the nervous system.

Born in Chicago on December 15, 1883, Dr. Hinton received his S. B. degree from Harvard in 1905 and his M.D. from Harvard Medical School in 1912. He was a professor at Simmons College from 1919 to 1953. He joined the staff of Harvard Medical School in 1923, serving as lecturer on bacteriology, and in 1949 was appointed clinical professor of bacteriology and immunology. He was also a special consultant to the United States Public Health Service, a director of the Committee on Research and Syphilis, Incorporated, and chief of Clinical Laboratories of the Boston Dispensary (1916-1952).

He is a member of the American Medical Association, the American Society of Clinical Pathologists, the Society of American Bacteriologists, the American Association for the Advancement of Science and the American Public Health Association and a fellow of the Massachusetts Medical Society.

CORRESPONDENCE

EPINEPHRINE IN ANGIOCARDIOGRAPHY

To the Editor: In the December 17 issue of the *Journal*, Dimond and Gonlubol report a case in which cardiac arrest followed angiocardiography and was treated with 1 cc. of 0.1 per cent epinephrine and then thoracotomy and cardiac massage, death occurring with irreversible ventricular fibrillation. This report should not pass without comment since the dose of epinephrine used as a cardiac stimulant was probably dangerously high; such a large amount frequently results in ventricular fibrillation, especially in the hypoxic heart.

In the past two years we have encountered ventricular fibrillation at cardiac resuscitation in 6 cases. In 2 the fibrillation followed and was probably caused by the intracardiac administration of 1 cc. of 0.1 per cent epinephrine used in the treatment of cardiac arrest. It was possible to defibrillate both these hearts electrically but neither patient survived.

Epinephrine is of unquestionable value in cardiac resuscitation but, as noted by Beecher and Linton in their report entitled "Epinephrine in Cardiac Stimulation" (*J.A.M.A.* **135**:90, 1947), should be used diluted and in low dosage. Epinephrine is commonly dispensed in ampoules containing 1 mg. of the drug, and unfortunately the use of the entire dose at once has been generally accepted as proper in cardiac resuscitation. It is our practice to give an intracardiac dose of 0.1 or 0.2 mg. diluted to 10 cc. or to start an intravenous drip of a solution of 1 mg. diluted to 500 cc. or more and regulate the speed of administration according to the response. Of course, unless an intracardiac dose can be given immediately on cessation of heart beat, preliminary restoration of circulation by cardiac massage will be required, since the anoxic heart cannot be expected to respond.

ROBERT S. SHAW, M.D.
Boston

SHIPS AND SEALING WAX

To the Editor: Re whichcraft — I am sure you recall the late Bret Harte's famous verse:

"Which I wish to remark,
And my language is plain,
Than for ways that are dark
And for tricks that are vain,
The heathen Chinee is peculiar:
Which the same I would rise to explain."

And then turning the page of your issue of January 14 I find a century-old item on porcupine quills.

Regarding the latter, there was recently at the Massachusetts General Hospital a patient who had acquired tetanus from a porcupine quill — also in the State of Maine. He had a shack near Mount Katahdin and a porcupine died under it. In getting this situation corrected he got a quill in his arm, and in due course the tetanus!

J. HOWARD MEANS, M.D.
Boston

MATERNAL MORTALITY IN CESAREAN SECTION

To the Editor: It has been called to our attention by Dr. H. R. Litchfield and his associates, of the Beth El Hospital, Brooklyn, New York, that in our paper, "Cesarean Sections at the Beth Israel Hospital, 1950–1953," which appeared in the October 29 issue of the *Journal*, we misquoted the maternal mortality from their article in the *Journal of the American Medical Association* (**151**:783-785, 1953).

We have reviewed the article carefully, and we find that Dr. Litchfield and his co-authors do not give any maternal-mortality statistics. Please rectify the error in Table 4 of our article.

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BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Handbook of Differential Diagnosis. By Harold T. Hyman, M.D., 12°, cloth, 716 pp. Philadelphia: J. B. Lippincott Company, 1953. $6.75.

This manual has been designed for ready reference use by physicians, students, interns and residents. The material is arranged alphabetically by conditions, diseases and subjects. The text is preceded by an enumeration of 1585 signs and symptoms. There is a valuable list of 90 pages devoted to occupational hazards, and a table of 14 pages on the clinical manifestations of industrial poisoning with nongaseous toxic substances. The book is well published and should prove useful to the readers for whom it was written.

Clinical Tropical Diseases. By A. R. D. Adams and B. G. Maegraith. From the School of Tropical Medicine, Liverpool, England. 8°, cloth, 508 pp., with 65 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $10.50.

This handbook gives the information needed for the diagnosis and treatment of diseases occurring primarily in the tropics. The conditions described are arranged in alphabetical order. This is a practical book, without references. The printing was done in Great Britain, and the publishing is excellent. The book should be in collections on the subject.

Inhalation Therapy and Resuscitation. By Meyer Saklad, M.D., director, Department of Anesthesiology, Rhode Island Hospital, Providence, Rhode Island. 8°, cloth, 343 pp., with 110 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $7.50. (Publication No. 156, *American Lecture Series.*)

This monograph presents a comprehensive survey of the various aspects of hypoxia and its treatment, and resuscitation. The literature is reviewed, and there is a bibliography of 402 references. The book should be in all medical libraries and in the collections of all persons interested in the subject.

Florida Medical Directory, 1953. Sixteenth edition. 4°, paper, 66 pp. Jacksonville, Florida: Florida Medical Association, 1953. $2.00.

This directory lists the membership of the state society by county societies and alphabetically. There is also a list of licensed nonresident doctors, and considerable other information.

Studies on Dried BCG Vaccine: November, 1952. 4°, paper, 99 pp., with 16 illustrations and 41 tables. Tokyo, Japan: Japan BCG Research Council, 1952.

Minimum requirements for dried BCG vaccine were promulgated in Japan for the first time in April, 1949. Three plants of the Japan Anti-Tuberculosis Association have been producing the vaccine in accordance with these requirements, subject to assay by the National Institute of Health of Japan. The Japan BCG Research Council, made up of 32 eminent physicians and scientists, was organized in September, 1949, and the results of their investigations to March, 1952, are reported in this monograph. The reports deal with the production, preservation, virulence and potency of the vaccine.

Roentgen Diagnosis of the Heart and Great Vessels. By Erich Zdansky, M.D., professor of roentgenology, University of Vienna, and director of the Central Roentgen Institute of the Allgemeinen Krankenhaus. Translated by Linn J. Boyd, M.D., professor and director of medicine, New York Medical College, Flower and Fifth Avenue Hospitals. First American edition. 4°, cloth, 500 pp., with 334 illustrations. New York: Grune and Stratton, 1953. $15.50.

The last German edition of this book was published in 1949, and Dr. Boyd has revised certain portions of the text to bring the material up to date. The chapters deal with the general technic of examination, the normal heart, atrophy, hypertrophy, and dilatation of single sections of the heart, the pathologic heart, diseases of the pericardium, the lesser circuit in cardiovascular disease, the aorta and the pulmonary artery and their pathologic alterations, and lobus venae azygos (Wrisbergi). The literature is surveyed, and there is a bibliography of 40 pages of references. The book is well published and should be in collections on cardiology.

Medicine. By A. E. Clark-Kennedy, M.D., F.R.C.P., fellow of Corpus Christi College, Cambridge, and physician to the London Hospital and dean of the Medical School. Volume 1. *The Patient and his Disease.* Second edition. 8°, cloth, 410 pp. Edinburgh: E. & S. Livingstone, Ltd., 1953. (Distributed by Williams and Wilkins, Baltimore, Maryland.) $6.00.

The author has revised the first volume of his book, first published in 1947 and now out of print, to bring it up to date and more in conformity with the second volume, *Diagnosis, Prevention and Treatment.* Changes have been made in the chapters on the body and mind, symptoms and signs, the normal and abnormal reactions of the body and mind, and on the nature of disease. The primary objective of the book is to emphasize the general principles underlying medicine as a whole. It is a personal book, outlining the ideas of the author without recourse to any literature. There are summaries for the chapters, and a good index. The publishing is excellent.

Slipped Capital Femoral Epiphysis. By Armin Klein, M.D., Robert J. Joplin, M.D., John A. Reidy, M.D., and Joseph Hanelin, M.D., Massachusetts General Hospital, Boston. 4°, cloth, 130 pp., with 77 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $6.75. (Publication No. 153, *American Lecture Series.*)

The authors review all the cases of slipped femoral epiphysis treated at the Massachusetts General Hospital since 1903 and compare the various methods of treatment. They became convinced that early diagnosis was essential and that early nailing in situ was the most satisfactory treatment. The book is practically an atlas with descriptive text. There are many full-page roentgenographic plates. The text deals with the roentgenographic standard for "normal" hips, diagnosis, treatment, operative technic and postoperative treatment. The book should be in all orthopedic collections.

Multiple Myeloma. By I. Snapper, M.D., director of medical education, Cook County Hospital, Chicago; Louis B. Turner, M.D., research assistant in medicine, Mount Sinai Hospital, New York City; and Howard L. Moscovitz, M.D., resident, Second Medical Service, Mount Sinai Hospital, New York City. 8°, cloth, 168 pp., with 43 illustrations and 15 tables. New York: Grune and Stratton, 1953. $6.50.

The authors of this monograph have covered the various aspects of multiple myeloma from diagnosis to treatment. Case histories are interspersed throughout the text. The literature has been surveyed, and there is a bibliography of 217 references. The publishing is excellent. (This type of monograph never gets out of date since it presents the latest knowledge of a subject to the date of publication.)

Practical X-Ray Treatment. By Arthur W. Erskine, M.D. Fourth edition. 8°, cloth, 195 pp., with 20 illustrations and 25 tables. Saint Paul, Minnesota: Bruce Publishing Company, 1953. $5.00.

The early chapters of this revised edition of a manual first published in 1931 deal with general subjects: current, apparatus, protection, measuring instruments, skin dosage and depth-dosage percentage, standard technics, scattering and distribution, determination of skin dosage and effects of x-rays on tissue. These are followed by chapters on skin disease, infections and inflammations, nonmalignant conditions, cancer and malignant conditions. Lists of references are appended to the chapters; there is a good index, and the publishing is excellent.

Introduction to Electron Microscopy. By Cecil E. Hall, associate professor of biophysics, Massachusetts Institute of Technology. 8°, cloth, 451 pp., with illustrations. New York: McGraw-Hill Book Company, Inc., 1953. $9.00 (*International Series in Pure and Applied Physics.*)

This textbook for students is based on five years' teaching experience at the Massachusetts Institute of Technology. Physics in general, the electrostatic and magnetic lenses and the electron microscope and its characteristics, methods and use are described in detail. The literature is reviewed, and lists of references are appended to the chapters. There are indexes of authors and subjects. The book is recommended to all medical libraries as a reference tool.

Stress Incontinence in the Female. By John C. Ullery, M.D., obstetrician and gynecologist, Pennsylvania Hospital, assistant professor in obstetrics and gynecology, Jefferson Medical College, associate in gynecology and obstetrics, Graduate School, University of Pennsylvania, chief of obstetrics and gynecology, Philadelphia General Hospital, and chief of obstetrics and gynecology, Delaware County Hospital, Drexel Hill, Pennsylvania. 4°, cloth, 149 pp., with 82 illustrations. New York: Grune and Stratton, 1953. $6.75.

This monograph presents a critical survey of the literature on the subject, with a discussion, in order, of embryology and anatomy, physiology of urination and continence, etiology, diagnosis, treatment and results of treatment. There is a bibliography of 137 references and a good index.

Die Nahbestrahlung. By Henri Chaoul, formerly, chief professor of roentgenology, Universität Berlin; and Felix Wachsmann, lecturer in medical physics, Universität Erlangen. Second edition. 8°, cloth, 225 pp., with 304 illustrations. Stuttgart: Georg Thieme, 1953. DM 39.— (Distributed by Grune and Stratton, New York.)

This monograph on proximity radiotherapy is comprehensive in scope. The text is divided into two parts, general and clinical. The former deals with physics and biology, technic and apparatus, dosage and its measurement, and the latter with the treatment of malignant tumors of the various organs and structures of the body to which the method is applicable. There are chapters on benign tumors of the skin and on inflammatory diseases. There is a bibliography of 695 references and a good index. The publishing is excellent. The book should be in all collections on the subject.

Die Zuckerkrankheit: Leitfaden für Studierender und Ärzte. By Prof. Dr. Ferdinand Bertram, physician-in-chief, Medizinischen Klinik des Allgemeinen Krankenhauses Langenhorn, Hamburg, and professor of internal medicine, Universität Hamburg. Fourth edition. 8°, cloth, 175 pp., with 25 illustrations and 9 tables. Stuttgart: Georg Thieme, 1953. DM 19.80. (Distributed by Grune and Stratton, New York.)

This new edition of a standard book has been completely revised. The text is divided into three main sections on metabolism, pathogenesis and treatment. There are also short chapters on the disease in children and on prognosis and prophylaxis.

Einführung in die Augenheilkunde. By Prof. Dr. Med. P. A. Jaensch, chief medical officer and physician-in-chief, Städtischen Augenklinik zu Essen, and professor, Medizinischen Akademie zu Düsseldorf. Second revised edition. 8°, cloth, 244 pp., with 197 illustrations. Stuttgart: Georg Thieme, 1953. DM 22.— (Distributed by Grune and Stratton, New York.)

The first edition of this typical German book was published in 1947. This new edition has been revised and brought up to date. The material is systematically arranged, beginning with the general subjects of anatomy and diagnosis, followed by diseases of the various parts of the eye. There is a good index, and the publishing is excellent in every way.

Atlas of Regional Dermatology. By Ernest K. Stratton, P.D., M.D., research associate, George Williams Hooper Foundation for Medical Research, University of California Medical Center, San Francisco; and Harry L. Arnold, Jr., M.D.; Maurice J. Costello, M.D.; Lewis A. Koplik, M.D.; and Paul Fasal, M.D. 4°, cloth, 274 pp., with 596 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $15.00.

Dr. Stratton has compiled this atlas of skin diseases based on regional distribution of the lesions. The material is arranged by regions: scalp, mouth, trunk, upper extremities, nails, lower extremities and vulva, penis and pubic and perianal areas. Dr. Arnold has written on leprosy, and Drs. Costello and Koplik on skin manifestations of the acute infectious diseases.

NONCLINICAL NOTES

SIR JACK DRUMMOND RESEARCH FELLOWSHIP

A memorial is being established in honor of the late Sir Jack Drummond to provide a Drummond Research Fellowship in Nutrition. Contributions may be made payable to the Drummond Memorial Fund, care of Professor L. A. Maynard, Cornell University, Ithaca, New York.

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the Boston City Hospital announces a series of lectures, to be held in the Dowling Amphitheater, Boston City Hospital, at 7 p.m., on the following dates:

February 23. Medicine and Mountains. Dr. Charles S. Houston, Exeter, New Hampshire.

March 2. Traumatic Lesions of the Growing Skeleton Other than Fractures and Dislocations. Dr. John Caffey, New York City.

March 9. Treatment of Hypertension in Medical Practice. Dr. Robert Wilkins, Boston.

March 16. Concepts of Congestive Heart Failure. Dr. John Bland, Burlington, Vermont.

April 8. To be announced. Dr. Leon Schiff, Cincinnati, Ohio.

April 20. Natural History of Bronchogenic Carcinoma. Dr. Leo G. Rigler, Minneapolis, Minnesota.

MASSACHUSETTS HOSPITAL SCHOOL ORTHOPEDIC ROUNDS

Orthopedic grand rounds will be held at the Bradford Memorial, Massachusetts Hospital School, Canton, from 9:30 to 10:30 a.m. on the following dates: February 20, March 20, April 17 and May 15. Dr. Albert B. Ferguson will be the speaker on March 20.

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

A regional meeting of the Central Region of the National Gastroenterological Association will be held in Milwaukee, on March 28. The scientific sessions will be held at the Hotel Schroeder at 2 p.m., after the semi-annual meeting of the National Council. All physicians are invited. A copy of the program may be obtained from the Secretary, National Gastroenterological Association, 33 West 60th Street, New York 23, New York.

AMERICAN CONGRESS OF PHYSICAL MEDICINE

The Eastern Sectional Meeting of the American Congress of Physical Medicine will be held at the Academy of Medicine in Newark on April 10, beginning with a tour of the Department of Physical Medicine and Rehabilitation, Veterans Administration Hospital, Orange, New Jersey, at 10 a.m. Further information may be obtained from Dr. Herman L. Rudolph, Section Secretary, 400 North Fifth Street, Reading, Pennsylvania.

AMERICAN GERIATRICS SOCIETY

The eleventh annual meeting of the American Geriatrics Society will be held at the Fairmount Hotel, San Francisco, June 17 through 19. Dr. Laurance W. Kinsell, Highland Alameda County Hospital, Oakland, California, will be in charge of local arrangements.

AMERICAN CANCER SOCIETY FELLOWSHIPS IN BIOMETRY AND EPIDEMIOLOGY

Several predoctoral and postdoctoral fellowships, supported by a grant from the American Cancer Society, are being offered at Yale University Graduate School to promote training and research in statistical methods as applied to the design of experiments and the collection and analysis of data applicable to the study of growth, the epidemiology of cancer and other chronic diseases and clinical research in cancer.

Applicants for the predoctoral fellowships are expected to enter the Graduate School as candidates for the degree of Doctor of Philosophy and will be given training in biology and statistics. The fellowships are awarded for three years, at $2000 a year.

Applicants for the postdoctoral fellowships must possess the degree of Doctor of Medicine, Philosophy or Science, and will receive training in biometry, biostatistics and other related subjects. Fellowships are awarded for one year and may be renewed for two additional years, at $3000 to $4500 a year.

Further information may be obtained from Professor E. Cuyler Hammond, director of graduate studies in biometry, 51 Hillhouse Avenue, Yale University, New Haven, Connecticut. All applications should be mailed before February 28, 1954.

AMERICAN COLLEGE OF SURGEONS SECTIONAL MEETING

A sectional meeting of the American College of Surgeons will be held at the Mount Royal Hotel, Montreal, Quebec, March 31 through April 2. Co-operating organizations will include the local hospitals, Montreal Ophthalmological Society, Section of Otolaryngology of the Montreal Medico-Chirurgical Society, Canadian Anaesthetists Society, Quebec Division, Society of Obstetricians and Gynecologists of Canada, Canadian Urological Society and the Societé d'Orthopédiques et Traumatologie de la Province de Quebec. Dr. Harry S. Morton, assistant professor of surgery, McGill University Faculty of Medicine, is chairman of the committee on arrangements.

NATIONAL VITAMIN FOUNDATION WILDER FELLOWSHIP

The National Vitamin Foundation has established a postdoctorate fellowship in memory of Dr. Russell M. Wilder, to promote the study of metabolism and nutrition. The fellowship will comprise three years, at yearly grants of $4500, $5000 and $5500, becoming effective September 1, 1954.

Applicants must furnish a letter from the executive officer and the head of the department of the institution where the work is to be done attesting to the fact that the candidate will be permitted and encouraged to do the necessary research, and the program of investigation must be outlined and approved by the preceptor. Application forms must be submitted before March 15. Notification to applicants will be made by July 1.

SOCIETY MEETINGS AND CONFERENCES

February 15–25. Consultation Clinics for Crippled Children. Page 180, issue of January 28.

February 15, March 1 and 15, April 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

February 15–20. Pan-American Academy of General Practice. Page 790, issue of November 5.

February 16. Tufts Medical Alumni Lecture. Page 181, issue of January 28.

February 16. South End Medical Club. Page 224, issue of February 4.

February 17. Massachusetts Medico-Legal Society. Page 224, issue of February 4.

February 19. New England Center Hospital House Officers' Association. Page 224, issue of February 4.

February 19–May 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

February 20 and 21. Mid-Winter Radiological Conference. Page 130, issue of January 21.

February 20, March 20, April 17 and May 15. Massachusetts Hospital School Orthopedic Rounds. Page 265.

February 23. Hampden District Medical Society. Page 224, issue of February 4.

February 23–25. College of Medical Evangelists Alumni Postgraduate Convention. Page 1044, issue of December 17.

February 23, March 2, 9, 16, April 8 and 20. Boston City Hospital House Officers' Association. Page 265.

February 26 and 27. New England Diabetes Association. Page 129, issue of January 21.

March 3 and April 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

March 11–13. American Orthopsychiatric Association. Page 129, issue of January 21.

March 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

March 22–25. American Academy of General Practice. Page 129, issue of January 21.

March 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

March 28. National Gastroenterological Association. Page 265.

March 31–April 2. American College of Surgeons Sectional Meeting. Notice above.

April 8–11. International Academy of Proctology. Page 130, issue of January 21.

April 9. New England Society of Anesthesiologists. Page 87, issue of January 14.

April 10. American Congress of Physical Medicine. Notice above.

April 29, 30 and May 1. American Goiter Association. Somerset Hotel, Boston.

May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

May 31–June 3. American Urological Association. Page xvii, issue of July 23.

June 17–19. American Geriatrics Society. Notice above.

July 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

July 23–29. International Cancer Congress. Page 914, issue of November 26.

September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

September 16–18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

District Medical Societies

ESSEX NORTH

May 12. 113th Annual Meeting. Andover Country Club, Andover.

HAMPDEN

February 23. Massachusetts Mutual Life Insurance Company, Springfield.

MIDDLESEX EAST

March 24.
May 11. Annual Meeting. (Harlow Dinner.)

Calendar for the Week Beginning Thursday, February 18

Thursday, February 18

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Difficult Sterility Problems. Dr. John Rock. Stearns Auditorium, New England Center Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

*8:15 p.m. Deaconess Medical Lecture. The Embolic and Constrictive Mechanisms in Coronary Artery Disease with Infarction. Dr. William Meissner. Joslin Auditorium, New England Deaconess Hospital.

(Notices concluded on page xxxiii)